BA

(12) UK Patent Application (19) GB (11) 2 295 616 (13) A

(43) Date of A Publication 05.06.1996

(21) Application No 9524401.8

(22) Date of Filing 29.11.1995

(30) Priority Data
(31) 9424264 (32) 01.12.1994 (33) GB

(71) Applicant(s)
Zeneca Limited

(Incorporated in the United Kingdom)

15 Stanhope Gate, LONDON, W1Y 6LN,
United Kingdom

(72) Inventor(s)
Andrew Austen Mortlock
Roger John Butlin

(74) Agent and/or Address for Service
Kevin Bill
Zeneca Pharmaceuticals, Intellectual Property Group, Intellectual Property Department, Mereside, Alderley Park, MACCLESFIELD, SK10 4TG, United Kingdom

(51) INT CL^6
C07D 241/22, A61K 31/495 31/50 31/505, C07D 237/20 239/69 403/12 405/12 409/12 // (C07D 403/12 207:27 241:22) (C07D 405/12 241:22 307:14) (C07D 409/12 241:22 333:32)

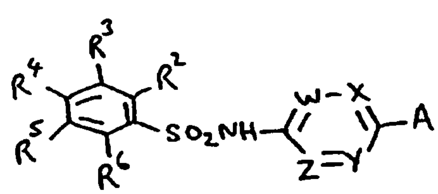
(52) UK CL (Edition O)
C2C CAA CSD C1173 C1200 C1228 C1341 C1472 C1511 C1590 C1600 C1620 C215 C22X C22Y C220 C221 C222 C225 C226 C25Y C250 C251 C252 C253 C254 C28X C29Y C292 C31Y C311 C313 C314 C32Y C321 C322 C332 C337 C338 C34Y C342 C351 C352 C355 C36Y C360 C362 C364 C366 C368 C37Y C373 C380 C385 C396 C51X C510 C511 C535 C539 C620 C660 C662 C672 C680 C682 C697 C699 C80Y C800 C802
U1S S1313 S1317 S1318 S1321 S1328 S2413 S2414 S2415 S2416

(56) Documents Cited
EP 0514133 A1

(58) Field of Search
Online: CAS ONLINE

(54) N-Diazine-benzenesulphonamide derivatives as endothelin receptor antagonists

(57) The invention concerns N-heterocyclyl sulphonamide derivatives of the formula I



I

in which the variables R^2-R^6 and the ring containing in, W, X, Y and Z and bearing substituent A have any of the meanings defined herein, and their pharmaceutically acceptable salts, and pharmaceutically compositions containing them. The novel compounds possess endothelin receptor antagonist activity and are useful in the treatment of diseases or medical conditions in which elevated or abnormal levels of endothelin play a significant causative role. The invention further concerns processes for the manufacture of the novel compounds and the use of the compounds in medical treatment.

GB 2 295 616 A

2295616

DIAZINE DERIVATIVES

The present invention relates to novel diazine derivatives and, more particularly, to novel N-heterocyclyl sulphonamides, and pharmaceutically-acceptable salts thereof, which possess endothelin receptor antagonist activity. These compounds are of value whenever such antagonist activity is desired, such as for research tools within pharmacological, diagnostic and related studies or in the treatment of diseases or medical conditions including, but not limited to, hypertension, pulmonary hypertension, cardiac or cerebral circulatory disease and renal disease, in warm-blooded animals (including man), in which elevated or abnormal levels of endothelin play a significant causative role. The invention also relates to pharmaceutical compositions of the novel compounds (and their salts) for use in treating said diseases or medical conditions, and to processes for the manufacture of the novel compounds. The invention further relates to the use of the novel compounds in treating one or more of the said diseases or medical conditions. A method of treating one or more of the said diseases or medical conditions using said compounds is also provided.

The endothelins are a family of endogenous 21 amino acid peptides comprising three isoforms, endothelin-1, endothelin-2 and endothelin-3. The endothelins are formed by cleavage of the Trp^{21}-Val^{22} bond of their corresponding proendothelins by a putative endothelin converting enzyme. The endothelins are among the most potent vasoconstrictors known and have a characteristic long duration of action. They exhibit a wide range of other activities including cell proliferation and mitogenesis, extravasation and chemotaxis, and also interact with a number of other vasoactive agents. They also have direct effects on the heart. Thus the biological profile of the endothelins is consistent with a pathophysiological role in the cardiovascular system. The endothelins also have actions on other physiological systems including the airways, gastro-intestinal tract, reproductive system, kidney, liver, central nervous system, neuro-endocrine system and the blood.

The endothelins are released from a range of tissue and cell sources including vascular endothelium, vascular smooth muscle, kidney, liver, uterus, airways, intestine and leukocytes. Release can be stimulated by hypoxia, shear stress, physical injury and a wide range of hormones and cytokines. Elevated endothelin levels have been found in a number of disease states in man including hypertension, pulmonary hypertension, pre-eclampsia, congestive heart failure, myocardial infarction, angina pectoris, acute and chronic renal failure, ischaemic stroke, subarachnoid haemorrhage, atherosclerosis, hypercholesterolaemia, cardiogenic and endotoxic shock, diabetes mellitus, Raynaud's disease, scleroderma, systemic sclerosis, Buerger's disease, rheumatoid arthritis, asthma, bronchitis, acute respiratory failure, liver cirrhosis, Crohn's disease, ulcerative colitis, certain cancers and after surgery.

Although a number of endothelin receptor antagonists are known, there is a continuing need for alternative antagonists. The present invention is based in part on this need and on our discovery of the unexpected antagonism of the endothelin receptor by certain N-heterocyclyl sulphonamides.

According to one aspect of the invention there is provided a compound of the formula I (set out hereinafter, together with the other chemical formulae indentified by Roman numerals) wherein

one of R^2 and R^3 is a group $-Y-R^1$ and the other of R^2 and R^3 is hydrogen in which

R^1 is selected from (1-10C)alkyl, (3-8C)cycloalkyl, (3-8C)cycloalkyl(1-6C)alkyl, (2-6C)alkenyl, (2-6C)alkynyl, 9-fluorenyl, phenyl(1-6C)alkyl, naphthyl, naphthyl(1-6C)alkyl, phenyl(2-6C)alkenyl, naphthyl(2-6C)alkenyl and a group Het.$(A^1)_m$- in which m is zero or the integer one, A^1 is (1-6C)alkylene or (2-6C)alkenylene and Het is a saturated or unsaturated heterocyclic ring of 5 to 14 ring atoms, one, two or three of the ring atoms being independently selected from

oxygen, nitrogen and sulphur and the remainder of the ring atoms being carbon, and in which heterocyclic ring a methylene group present is optionally replaced by a carbonyl group and/or an NH group present optionally bears an (1-4C)alkyl, phenyl or phenyl(1-4C)alkyl group; and

Y is selected from a direct bond and a group of the formula -O-, $-NR^7$.CO.O-, $-NR^7$.CO.S-, $-NR^7.CO.NR^7$-, $-NR^7.SO_2$-, -CO-, -CO.S-, $-CS.NR^7$-, -CO.O-, $-CO.NR^7$-, $-NR^7$-, $-NR^7$.CO-, $-SO_2$.O-, $-SO_2.NR^7$- and $-S(O)_n$- in which n is zero, 1 or 2 and R^7 is hydrogen or (1-4C)alkyl;

or R^1 is phenyl and Y is selected from a group of the formula -O-, $-NR^7$.CO.O-, $-NR^7$.CO.S-, $-NR^7.CO.NR^7$-, $-NR^7.SO_2$-, -CO-, -CO.S-, $-CS.NR^7$-, -CO.O-, $-CO.NR^7$-, $-NR^7$-, $-NR^7$.CO-, $-SO_2$.O-, $-SO_2.NR^7$- and $-S(O)_n$- in which n is zero, 1 or 2 and R^7 is hydrogen or (1-4C)alkyl;

and wherein an alkyl, cycloalkyl, alkenyl, alkynyl, phenyl or naphthyl group of R^1, or an alkylene or alkenylene group of A^1, or a heterocyclic ring Het optionally bears one, two or three substituents independently selected from halogeno, (1-6C)alkoxy, dihalogeno(1-6C)alkoxy, trihalogeno(1-6C)alkoxy, (2-6C)alkenyloxy, phenyl(1-6C)alkoxy, hydroxy, mercapto, nitro, carboxy, (1-6C)alkoxycarbonyl, (2-6C)alkenyloxycarbonyl, phenyloxycarbonyl, phenyl(1-4C)alkoxycarbonyl, (1-6C)alkanoyl, phenyl, benzoyl, (1-6C)alkylthio, (1-6C)alkylsulphinyl, (1-6C)alkylsulphonyl, phenylthio, phenylsulphinyl, phenylsulphonyl, phenyl(1-6C)alkylthio, phenyl(1-6C)alkylsulphinyl, phenyl(1-6C)alkylsulphonyl, (1-6C)alkanoylamino, trifluoroacetyl, trifluoroacetamido, N-[(1-4C)alkyl]trifluoroacetamido, benzamido, N-[(1-4C)alkyl]benzamido, carbamoyl, (1-4C)alkylcarbamoyl, di-(1-4C)alkylcarbamoyl, phenylcarbamoyl, sulphamoyl, N-(1-4C)alkylsulphamoyl, N,N-di-(1-4C)alkylsulphamoyl, N-phenylsulphamoyl, (1-6C)alkanesulphonamido, benzenesulphonamido, ureido, 3-(1-6C)alkylureido, 3-phenylureido, thioureido, 3-(1-6C)alkylthioureido, 3-phenylthioureido and a group of the formula -NRaRb in which Ra and Rb are independently selected from hydrogen, (1-6C)alkyl, phenyl(1-4C)alkyl and (1-6C)alkyl bearing a carboxy or

(1-4C)alkoxycarbonyl group, or the group -NRaRb taken together complete a 1-pyrrolidinyl, 2-oxo-1-pyrrolidinyl, 1-piperidinyl, 2-oxo-1-piperidinyl or morpholino ring;

and wherein in addition a phenyl, naphthyl or heterocyclic ring Het of R^1 may optionally bear one, two or three substituents independently selected from (1-6C)alkyl, amino(1-6C)alkyl, hydroxy(1-6C)alkyl, (1-4C)alkoxy(1-6C)alkyl, N-[(1-4C)alkyl]amino(1-6C)alkyl, N,N-[di(1-4C)alkyl]amino(1-6C)alkyl, (2-6C)alkenyl, 2-[(1-6C)alkoxycarbonyl]ethenyl, 2-phenylethenyl, (2-6C)alkynyl, (1-6C)alkoxycarbonylethynyl, phenylethynyl, halogeno(1-6C)alkyl, (1-4C)alkylthio(1-4C)alkyl, (1-4C)alkylsulphinyl(1-4C)alkyl, (1-4C)alkylsulphonyl(1-4C)alkyl, (3-6C)cycloalkyl, (3-8C)cycloalkyl(1-6C)alkyl and phenyl(1-6C)alkyl;

and wherein a phenyl ring of a substituent on R^1 may itself optionally bear one or two (1-4C)alkyl, (1-4C)alkoxy, halogeno, trifluoromethyl, nitro or cyano substituents;

R^4 is selected from hydrogen, fluoro, amino and hydroxy;

R^5 and R^6 are independently selected from hydrogen, (1-6C)alkyl, (1-6C)alkoxy, halogeno, trifluoromethyl, cyano, nitro, amino, (1-6C)alkylamino, di-(1-6C)alkylamino, (1-6C)alkanoylamino, hydroxy, mercapto, (1-6C)alkylthio, (1-6C)alkanoyl, trifluoroacetyl, trifluoroacetylamino, (1-6C)alkanesulphonamido, 1-pyrrolidinyl, 2-oxo-1-pyrrolidinyl, 1-piperidinyl, 2-oxo-1-piperidinyl or morpholino; and

the ring containing W, X, Y and Z and bearing substituent A is selected from:

(a) a ring in which W is nitrogen; X is CH; Y is nitrogen; and Z is CRy in which Ry is hydrogen, halogeno, (1-4C)alkyl or (1-4C)alkoxy; and substituent A is hydrogen, halogeno, (1-4C)alkyl, methoxy, ethoxy, methylthio, ethylthio, trifluoromethyl or ethynyl;

(b) a ring in which W is CRz in which Rz is hydrogen, halogeno, (1-4C)alkyl or (1-4C)alkoxy; X is nitrogen; Y is nitrogen; and Z is CH; and substituent A is halogeno, (1-4C)alkyl, methoxy, ethoxy, methylthio, ethylthio, trifluoromethyl or ethynyl; and

(c) a ring in which W and X are both nitrogen; Y is CH; and Z is CRx in which Rx is hydrogen, methyl, methoxy or ethoxy; and substituent A is halogeno, (1-4C)alkyl, methoxy, ethoxy, methylthio, ethylthio, trifluoromethyl or ethynyl;

or a pharmaceutically-acceptable salt thereof; but excluding the compound N-(6-chloropyridazin-3-yl)-2-methylbenzenesulphonamide and pharmaceutically acceptable salts thereof.

It will be appreciated that, depending on the nature of the substituents, certain of the formula I compounds may possess one or more chiral centres and may be isolated in one or more racemic or optically active forms. It is to be understood that the present invention concerns any form of such a compound of formula I which possesses the afore-mentioned useful pharmacological properties, it being well known to make optically active forms, for example by synthesis from suitable chiral intermediates or by resolution, and how to determine their pharmacological properties, for example by use of the tests described hereinafter.

It will also be appreciated that a compound of formula I may exhibit polymorphism, that a compound of formula I may form a solvate and that a compound of formula I may exist in more than one tautomeric form. It is to be understood that the present invention also concerns any polymorphic form, any tautomer or any solvate, or any mixture thereof, which possesses endothelin receptor antagonist activity.

It is further to be understood that generic terms such as "alkyl" and "alkylene", include both straight and branched chain variants when the carbon numbers permit.

However, when a particular radical such as "propyl" is given, it is specific to the straight chain variant, branched chain variants such as "isopropyl" being specifically named when intended. The same convention applies to other radicals.

It is also to be understood that, where a phenyl or naphthyl group of R^1 is referred to, this includes a phenyl or naphthyl group which forms part of a phenylalkyl, phenylalkenyl, naphthylalkyl, naphthylalkenyl or 9-fluorenyl group. Also, when a phenyl ring of a substituent on R^1 is referred to, this includes the phenyl ring of a benzoyl, benzamido or benzenesulphonamido group. Furthermore where an alkyl, cycloalkyl or alkenyl group of R^1 is referred to, this includes an alkyl group which forms part of a cycloalkylalkyl, phenylalkyl or naphthylalkyl group; a cycloalkyl group of a cycloalkylalkyl group; and an alkenyl group of a phenylalkenyl or naphthylalkenyl group.

Particular values for R^1 include, by way of example,
for (1-10C)alkyl: (1-6C)alkyl, for example (1-4C)alkyl, such as methyl, ethyl, propyl, isopropyl and sec-butyl;
for (3-8C)cycloalkyl: norbornyl or (3-6C)cycloalkyl, such as cyclopropyl, cyclobutyl and cyclopentyl;
for (3-8C)cycloalkyl(1-6C)alkyl: (3-5C)cycloalkyl(1-2C)alkyl, such as cyclopropylmethyl, cyclopropylethyl, cyclobutylmethyl and cyclopentylmethyl;
for (2-6C)alkenyl: (2-4C)alkenyl, such as vinyl, allyl, 1-propenyl and 2-butenyl;
for (2-6C)alkynyl: (2-4C)alkynyl, such as ethynyl, 1-propynyl, 2-propynyl and 1-butynyl;
for phenyl(1-6C)alkyl: phenyl(1-4C)alkyl, such as benzyl, 1-phenylethyl and 2-phenylethyl;
for naphthyl(1-6C)alkyl: naphthyl(1-4C)alkyl, such as naphth-1-ylmethyl, naphthyl-2-ylmethyl, 1-(naphth-1-yl)ethyl and 2-(naphth-1-yl)ethyl;
for phenyl(2-6C)alkenyl: phenyl(2-4C)alkenyl, such as 2-phenylethenyl and 3-phenylpropen-1-yl; and
for naphthyl(2-6C)alkenyl: naphthyl(2-4C)alkenyl, such as

2-(naphth-1-yl)ethenyl and 3-(naphth-1-yl)propen-1-yl.

Particular values for a heterocyclic group Het when R^1 is a group Het.$(A^1)_m$- include, for example, pyridyl, pyrimidinyl, pyrazinyl, pyridazinyl, triazinyl, thienyl, furyl, tetrahydrofuryl, tetrahydrothienyl, pyranyl, pyrrolyl, imidazolyl, pyrazolyl, thiazolyl, isothiazolyl, oxazolyl, isoxazolyl, indolyl, indazolyl, quinolyl, isoquinolyl, phthalazinyl, naphthyridinyl, quinoxazinyl, cinnolinyl, carbazolyl, beta-carbolinyl, phenanthridinyl, acridinyl, phenanthrolinyl, phenazinyl, phenothiazinyl, phenoxazinyl, chromanyl, isochromanyl, pyrrolidinyl, pyrrolinyl, imidazolidinyl, pyrazolidinyl, pyrazolinyl, piperidinyl, piperazinyl, indolinyl, isoindolinyl, morpholinyl, thiomorpholinyl, quinuclidinyl, 2-oxo-hexahydroazepinyl, 2-oxopyrrolidinyl, 2-oxo-tetrahydrothienyl, N-methylpiperidinyl, N-benzylpiperidinyl and N-methylmorpholinyl. It will be appreciated that the group Het may be attached to $(A^1)_m$ (or attached directly to Y if m is zero or attached directly to the phenyl ring of formula I if m is zero and Y is a direct bond) by carbon or nitrogen where valences permit.

Particular values for A^1 when R^1 is a group Het.$(A^1)_m$- include, for example,
for (1-6C)alkylene: (1-4C)alkylene, such as methylene, ethylene, trimethylene and propylene; and
for (2-4C)alkenylene: vinylene and propenylene.

Particular values for an optional substituent on an alkyl, cycloalkyl, cycloalkylalkyl, alkenyl, alkynyl, phenyl or naphthyl group of R^1, or an alkylene or alkenylene group of A^1, or a heterocyclic ring Het of R^1, include, for example:

for halogeno: fluoro, chloro, bromo and iodo;
for (1-6C)alkoxy: (1-4C)alkoxy, such as methoxy, ethoxy and propoxy;
for di- or trihalogeno(1-6C)alkoxy: di- or tri-halogeno(1-4C)alkoxy, such as difluoromethoxy, trifluoroethoxy, 2,2,2-trifluoroethoxy, 3,3,3-trifluoropropoxy and pentafluoroethoxy;

for (2-6C)alkenyloxy: (2-4C)alkenyloxy, such as vinyloxy, allyloxy, 1-propenyloxy and 2-butenyloxy;
for phenyl(1-6C)alkoxy: phenyl(1-4C)alkoxy, such as benzyloxy, 1-phenylethoxy, 2-phenylethoxy, 2-phenylpropoxy and 3-phenylpropoxy;
for (1-6C)alkoxycarbonyl: (1-4C)alkoxycarbonyl, such as methoxycarbonyl, ethoxycarbonyl and propoxycarbonyl;
for (2-6C)alkenyloxycarbonyl: allyloxycarbonyl, 2-methyl-2-propenyloxycarbonyl and 3-methyl-3-butenyloxycarbonyl;
for phenyl(1-4C)alkoxycarbonyl: benzyloxycarbonyl, 1-phenylethoxycarbonyl and 2-phenylethoxycarbonyl;
for (1-6C)alkanoyl: (1-4C)alkanoyl, such as formyl, acetyl and propionyl;
for (1-6C)alkylthio: (1-4C)alkylthio, such as methylthio and ethylthio;
for (1-6C)alkylsulphinyl: (1-4C)alkylsulphinyl, such as methylsulphinyl and ethylsulphinyl;
for (1-6C)alkylsulphonyl: (1-4C)alkylsulphonyl, such as methylsulphonyl and ethylsulphonyl;
for phenyl(1-6C)alkylthio: phenyl(1-4C)alkylthio, such as phenylmethylthio and 2-phenylethylthio;
for phenyl(1-6C)alkylsulphinyl: phenyl(1-4C)alkylsulphinyl, such as phenylmethylsulphinyl and 2-phenylethylsulphinyl;
for phenyl(1-6C)alkylsulphonyl: phenyl(1-4C)alkylsulphonyl, such as phenylmethylsulphonyl and 2-phenylethylsulphonyl;
for (1-6C)alkanoylamino: (1-4C)alkanoylamino, such as formamido, acetamido and propionamido;
for N-[(1-4C)alkyl]trifluoroacetamide: N-methyltrifluoroacetamide and N-ethyltrifluoroacetamide;
for N-[(1-4C)alkyl]benzamido: N-methylbenzamido and N-ethylbenzamido;
for (1-4C)alkylcarbamoyl: N-methylcarbamoyl and N-ethylcarbamoyl;
for di(1-4C)alkylcarbamoyl: N,N-dimethylcarbamoyl and N,N-diethylcarbamoyl;
for N-(1-4C)alkylsulphamoyl: N-methylsulphamoyl and N-ethylsulphamoyl
for N,N-di(1-4C)alkylsulphamoyl: N,N-dimethylsulphamoyl and N,N-diethylsulphamoyl;
for (1-6C)alkanesulphonamido: (1-4C)alkanesulphonamido, such as methanesulphonamido and ethanesulphonamido;

for 3-(1-6C)alkylureido: 3-(1-4C)alkylureido, such as 3-methylureido, 3-ethylureido and 3-propylureido; and
for 3-(1-6C)alkylthioureido: 3-(1-4C)alkylthioureido, such as 3-methylthioureido, 3-ethylthioureido and 3-propylthioureido.

A particular value for an optional substituent on a phenyl, naphthyl or heterocyclic group Het includes, for example:

for (1-6C)alkyl: (1-4C)alkyl, such as methyl, ethyl and propyl;
for amino(1-6C)alkyl: amino(1-4C)alkyl, such as aminomethyl and 2-aminoethyl;
for hydroxy(1-6C)alkyl: hydroxy(1-4C)alkyl, such as hydroxymethyl, 1-hydroxyethyl and 2-hydroxyethyl;
for (1-4C)alkoxy(1-6C)alkyl: (1-2C)alkoxy(1-4C)alkyl, such as methoxymethyl, ethoxymethyl, 1-methoxyethyl, 2-methoxyethyl, 2-ethoxyethyl and 3-methoxypropyl;
for N-[(1-4C)alkyl]amino(1-6C)alkyl: N-[(1-2C)alkylamino(1-4C)alkyl, such as methylaminomethyl and methylaminoethyl;
for N,N-[di(1-4C)alkyl]amino(1-6C)alkyl: N,N-[di(1-2C)alkyl]amino-(1-4C)alkyl, such as dimethylaminomethyl and 2-(dimethylamino)ethyl;
for (2-6C)alkenyl: (2-4C)alkenyl, such as vinyl and allyl;
for (1-6C)alkoxycarbonyl(2-6C)alkenyl: (1-4C)alkoxycarbonyl(2-4C)alkenyl, such as 2-methoxycarbonylethenyl and 2-ethoxycarbonylethenyl;
for (2-6C)alkynyl: (2-4C)alkynyl, such as ethynyl and 2-propynyl;
for (1-6C)alkoxycarbonyl(2-6C)alkynyl: (1-4C)alkoxycarbonyl(2-4C)alkynyl, such as methoxycarbonylethynyl and ethoxycarbonylethynyl;
for halogeno(1-6C)alkyl: halogeno(1-4C)alkyl, such as chloromethyl, bromomethyl, fluoromethyl, dichloromethyl, difluoromethyl, trifluoromethyl, 2,2,2-trifluoroethyl and pentafluoroethyl;
for (1-4C)alkylthio(1-4C)alkyl: methylthiomethyl, 1-methylthioethyl, 2-methylthioethyl, 2-methylthioprop-2-yl, ethylthiomethyl,1-ethylthioethyl, 2-ethylthioethyl and 2-ethylthioprop-2-yl;
for (1-4C)alkylsulphinyl(1-4C)alkyl: methylsulphinylmethyl,

1-methylsulphinylethyl, 2-methylsulphinylethyl, 2-methylsulphinylprop-2-yl, ethylsulphinylmethyl, 1-ethylsulphinylethyl, 2-ethyl-sulphinylethyl and 2-ethylsulphinylprop-2-yl;
for (1-4C)alkylsulphonyl(1-4C)alkyl: methylsulphonylmethyl, 1-methylsulphonylethyl, 2-methylsulphonylethyl, 2-methylsulphonylprop-2-yl, ethylsulphonylmethyl, 1-ethylsulphonylethyl, 2-ethyl-sulphonylethyl and 2-ethylsulphonylprop-2-yl;
for (3-6C)cycloalkyl: cyclopropyl, cyclobutyl and cyclopentyl;
for (3-8C)cycloalkyl(1-6C)alkyl: (3-5C)cycloalkyl(1-2C)alkyl, such as cyclopropylmethyl, cyclopropylethyl, cyclobutylmethyl and cyclopentylmethyl; and
for phenyl(1-6C)alkyl: phenyl(1-4C)alkyl, such as benzyl, 1-phenylethyl and 2-phenylethyl.

A particular value for Ra or Rb includes, by way of example,
for (1-6C)alkyl: (1-4C)alkyl, such as methyl, ethyl and propyl;
for (1-6C)alkyl bearing a carboxy or (1-4C)alkoxycarbonyl group: (1-4C)alkyl bearing a carboxy or (1-2C)alkoxycarbonyl group, such as carboxymethyl, carboxyethyl, methoxycarbonylmethyl, methoxycarbonylethyl, ethoxycarbonylethyl, ethoxycarbonylethyl, methoxycarbonylpropyl and ethoxycarbonylpropyl;
for phenyl(1-4C)alkyl: benzyl, 1-phenylethyl and 2-phenylethyl.

A particular value for a substituent on a phenyl ring of a substituent of R^1 includes, for example,
for (1-4C)alkyl: methyl or ethyl;
for (1-4C)alkoxy: methoxy or ethoxy; and
for halogeno: fluoro, chloro, bromo and iodo.

A particular value for R^5 or R^6 includes, by way of example,
for (1-6C)alkyl: (1-4C)alkyl, such as methyl and ethyl;
for (1-6C)alkoxy: (1-4C)alkoxy, such as methoxy and ethoxy;
for halogeno: fluoro, chloro, bromo and iodo;
for (1-6C)alkylamino: (1-4C)alkylamino, such as methylamino and

ethylamino;
for di-(1-6C)alkylamino: di-(1-4C)alkylamino, such as dimethylamino, N-methyl-N-ethylamino and diethylamino;
for (1-6C)alkanoylamino: (1-4C)alkanoylamino, such as formamido, acetamido and propionamido;
for (1-6C)alkylthio: (1-4C)alkylthio, such as methylthio and ethylthio; and for (1-6C)alkanesulphonamido: (1-4C)alkanesulphonamido, such as methanesulphonamido and ethanesulphonamido.

Particular values for Ry and Rz include, for example, for halogeno: fluoro, chloro, bromo and iodo; for (1-4C)alkyl: methyl, ethyl and propyl; and for (1-4C)alkoxy: methoxy, ethoxy and propoxy.

Particular values for substituent A include, for example, for halogeno: chloro, bromo and iodo; and for (1-4C)alkyl: methyl, ethyl and propyl.

Values for Y of particular interest include, for example, a direct bond, -O-, -S-, $-SO_2-$, $-NR^7-$, -CO-, $-CS-NR^7-$, -CO.O- and $-CO.NR^7-$, especially the latter three groups. Preferred values for Y include, for example, -CO.O- and $-CO.NR^7-$, especially $-CO.NR^7-$, and more especially -CO.NH-.

Values of R^1 of interest include, for example, (1-10C)alkyl, (3-6C)cycloalkyl, (3-8C)cycloalkyl(1-6C)alkyl, phenyl, phenyl(1-6C)alkyl, naphthyl(1-6C)alkyl and a group Het.$(A^1)_m$- in which m is zero or the integer one, A^1 is (1-4C)alkylene and Het is a saturated or unsaturated heterocyclic ring of 5 or 6 ring atoms, 1 or 2 of said ring atoms being independently selected from oxygen, nitrogen and sulphur and the remainder being carbon, and in which heterocyclic ring a methylene present is optionally replaced by a carbonyl group and/or an NH group present optionally bears an (1-4C)alkyl, phenyl or phenyl(1-4C)alkyl group; and in which an alkyl, cycloalkyl, phenyl or naphthyl group of R^1, or an alkylene group of A^1, or a heterocyclic ring Het, optionally bears one or two substituents independently selected from any of those defined above.

Values for R^1 of particular interest include, for example, (1-10C)alkyl, phenyl, halogenophenyl, phenyl(1-4C)alkyl, phenyl(1-4C)alkyl bearing one or two (1-4C)alkyl, (1-4C)alkoxy, (1-4C)alkylthio, halogeno, amino, benzyl or phenyl groups in the phenyl ring, phenyl(1-4C)alkyl bearing an (1-4C)alkoxycarbonyl group on the alkyl chain, (3-8C)cycloalkyl, 2-hydroxycyclohexyl, (3-6C)cycloalkylmethyl, 2-oxo-1-pyrrolidinyl(1-4C)alkyl, tetrahydrofurfuryl, 2-oxo-tetrahydrothien-3-yl, 9-fluorenyl and norbornyl.

Preferred values for R^1 include, for example, (1-10C)alkyl, phenyl(1-2C)alkyl optionally bearing one or two (1-2C)alkyl, (1-2C)alkoxy, (1-2C)alkylthio, halogeno, amino, benzyl or phenyl groups in the phenyl ring and optionally bearing an (1-2C)alkoxycarbonyl group on the alkyl chain, (3-6C)cycloalkyl, (3-6C)cycloalkylmethyl and 9-fluorenyl.

A preferred value for R^4 includes, for example, hydrogen.

A preferred value for R^5 or R^6 includes, for example, hydrogen, (1-4C)alkyl, (1-4C)alkoxy, halogeno and nitro.

A preferred value for substituent A includes, for example, halogeno, especially chloro or bromo.

A preferred value for Ry or Rz includes, for example, methoxy.

Individual groups of compounds of the invention which are of interest, include, for example,
(i) compounds of the formula Ia in which A^a is hydrogen, halogeno, (1-4C)alkyl, methoxy, ethoxy, methylthio, ethylthio, trifluoromethyl or ethynyl; B^a is hydrogen, halogeno, (1-4C)alkyl or (1-4C)alkoxy; and R^2 to R^6 have any of the values defined above; or a pharmaceutically acceptable salt thereof;

(ii) compounds of the formula Ib in which A^b is halogeno, (1-4C)alkyl, methoxy, ethoxy, methylthio, ethylthio, trifluoromethyl or ethynyl; B^b is hydrogen, halogeno, (1-4C)alkyl or (1-4C)alkoxy; and R^2 to R^6 have any of the values defined above; or a pharmaceutically acceptable salt thereof; and

(iii) compounds of the formula Ic in which A^c is halogeno, (1-4C)alkyl, methoxy, ethoxy, methylthio, ethylthio, trifluoromethyl or ethynyl; Bc is hydrogen, methyl, methoxy or ethoxy; and R^2 to R^6 have any of the values defined above; or a pharmaceutically acceptable salt thereof; but excluding the compound N-(6-chloropyridazin-3-yl)-2-methylbenzenesulphonamide and pharmaceutically acceptable salts thereof.

Within groups (i), (ii) and (iii), particular independent sub-groups of compounds include, for example, compounds of the formula IIa, IIb, IIc, IId, IIe and IIf, in which R^1, R^4, R^5, R^6, Y, A^a, A^b, A^c, B^a, B^b and Bc have any of the meanings defined above.

Preferably within groups (i), (ii) and (iii), one of R^2 and R^3 is a group $-Y-R^1$ in which Y is a group -CO.O- or $-CO.NR^7-$, in which R^7 is hydrogen or (1-4C)alkyl, and the other of R^2 and R^3 is hydrogen; and R^4, R^5 and R^6 are all hydrogen. Similarly, in the sub-groups of formula IIa, IIb, IIc, IId, IIe and IIf, Y is preferably -CO.O- or $-CO.NR^7-$ in which R^7 is as defined above. Within the groups of compounds of formula Ia and IIa, further sub-groups of compounds which are particularly preferred are those in which A^a is halogeno (especially chloro or bromo) and B^a is methoxy. Within the groups of compounds of formula Ib and IIb, further sub-groups of compounds which are particularly preferred are those in which A^b is halogeno (especially chloro or bromo) and B^b is methoxy. Within the groups of compounds of formula Ic and IIc, further sub-groups of compounds which are particularly preferred are those in which A^c is halogeno (especially chloro or bromo) and Bc is hydrogen.

Further groups of compounds of the invention may be obtained by combining any of the abovementioned particular or generic values for

the radicals.

Compounds of the invention which are of particular interest include, for example, the specific embodiments set out hereinafter in the accompanying Examples. Of these, the compounds of formula I disclosed in Examples 1, 3, 4, 13, 21, 34, 37, 41, 46, 49 and 57 are of special interest and these compounds, or a pharmaceutically-acceptable salt thereof, are provided as a further feature of the invention.

Suitable pharmaceutically-acceptable salts include, for example, salts with alkali metal (such as sodium, potassium or lithium), alkaline earth metals (such as calcium or magnesium), ammonium salts, and salts with organic bases affording physiologically acceptable cations, such as salts with methylamine, dimethylamine, trimethylamine, piperidine and morpholine. In addition, for those compounds which are sufficiently basic suitable pharmaceutically-acceptable salts include, pharmaceutically-acceptable acid-addition salts with hydrogen halides, sulphuric acid, phosphoric acid and with organic acids such as citric acid, maleic acid, methanesulphonic acid and p-toluenesulphonic acid. Alternatively, the compound of formula I may exist in a zwitterionic form.

The compounds of formula I may be obtained by standard procedures of organic chemistry well known in the art for the production of structurally analogous compounds. Such procedures are provided as a further feature of the invention and include, by way of example, the following procedures in which the generic radicals have any of the values given above, unless stated otherwise.

(a) an amine (or an alkali metal salt thereof) of the formula III is reacted with a sulphonyl halide of formula IV in which Hal. is a halogeno group (for example, fluoro, chloro, bromo or iodo) in a suitable solvent.

A suitable solvent includes, for example, pyridine. A catalyst, such as 4-dimethylaminopyridine or 4-pyrrolidinopyridine, may be added to assist the coupling reaction. The reaction is generally

carried out at a temperature in the range of, for example, 0°C to 120°C and more generally 20°C to 120°C. Alternatively a solvent such as dichloromethane, chloroform, dimethoxyethane, tetrahydrofuran, dioxan, N,N-dimethylformamide or N-methyl-2-pyrrolidone may be used in the presence of a suitable inorganic base, such as sodium or potassium carbonate (which may be present as an aqueous solution) or an organic base, for example a teriary amine such as pyridine or triethylamine. When the alkali metal salt of the amine of formula II is used, this may be formed, for example with the use of a suitable base such as lithium diisopropylamide at a temperature, for example, about -60°C, or sodium hydride at, for example, ambient temperature, prior to the addition of the sulphonyl halide. However it will be appreciated that the reaction of a sulphonyl halide with an amine to form a sulphonamide (and the type of solvents and conditions used therein) is well-known in the art.

Alternatively an amine (or alkali metal salt thereof) of the formula III may be reacted with a sulphonate of the formula IVa in which Re is an electron deficient phenyl group, for example a phenyl group bearing one or more electron-withdrawing groups, such as nitro or cyano, in a sutiable solvent. A preferred value for Re includes, for example, 4-nitrophenyl. The reaction is carried out under similar conditons to those described above.

(b) for a compound of the formula I in which V is nitrogen, a compound of the formula V in which L is a suitable leaving group (such as chloro, bromo, iodo, methanesulphonyloxy or p-toluenesulphonyloxy) is reacted with a sulphonamide of the formula VI. The reaction is generally carried out in the presence of a base, such as an alkali metal hydroxide or alkoxide (such as sodium hydroxide, potassium hydroxide, sodium methoxide, potassium methoxide, sodium ethoxide, potassium ethoxide or potassium tert-butoxide) or an alkali metal hydride (such as sodium or potassium hydride), or an organic base such as diisopropylethylamine. The reaction may also be carried out using a pre-formed alkali metal salt of a compound of the formula VI. A suitable inert organic solvent is usually employed, for example, N,N-dimethylformamide or N-methylpyrrolidone. The reaction is generally carried out at a temperature in the range of, for example,

20°C to 120°C.

Sulphonyl halides of formula IV are well known in the art or may be obtained by conventional procedures, for example as illustrated in the Examples hereinafter or by analogy therewith. They may also be obtained by reaction of an amine of formula VII with sodium nitrite and hydrochloric acid to form a diazonium salt, followed by reaction of the diazonium salt with sulphur dioxide in dioxan and work-up with a haloacid. Compounds of the formula IVa may be obtained from the corresponding sulphonyl chloride by reaction with the appropriate phenol (Re.OH) using conventional procedures, for example, by heating in pyridine. Compounds of formula III and V are commercially available or are also well-known in the art, being described in standard works of heterocyclic chemistry such as those edited by Elderfield or Wiessberger, and others can be obtained by analogy therewith using standard procedures of organic chemistry. The sulphonamides of formula VI may be obtained from corresponding compounds of formula IV using standard procedures, for example by using aqueous ammonia.

(c) for a compound of the formula I in which Y is a group of the formula $-NR^7.CO.O-$, $-NR^7.CO.S-$, $NR^7.CO.NH-$, $-NR^7.SO_2-$, $-NR^7-$ or $-NR^7.CO-$, a compound of formula VIIIa or VIIIb is alkylated or acylated with an appropriate alkylating or acylating agent. For example an acylating or alkylating agent of the formula $R^1.O.CO.L^1$, $R^1.S.CO.L^1$, $R^1.NCO$, $R^1.SO_2.L^1$, $R^1.L^1$ or $R^1.CO.L^1$ may be used, in which L^1 is a suitable leaving group, in the presence of a suitable base, such as pyridine or triethylamine. A catalyst, such as 4-dimethylaminopyridine or 4-pyrrolidinopyridine, may be added to assist the reaction. It will be appreciated that L^1 can take various values, and that conventional procedures may be used to carry out the reaction. For example, L^1 may be halogeno (such as chloro, bromo or iodo). For a compound in which Y is $-NR^7.CO-$, a carboxylic acid of the formula $R^1.CO.OH$ may be used (or a reactive derivative thereof such as the chloride, bromide, anhydride or mixed anhydride with formic or acetic acid). When the free acid form is used, the reaction is generally carried out in the presence of a suitable dehydrating agent, for example a carbodiimide (such as

dicyclohexylcarbodiimide or 3-(3-dimethylaminopropyl)-1-ethylcarbodiimide) or 1,1'-carbonyldiimidazole. In general the alkylation or acylation is carried out in a suitable inert diluent or solvent, such as those mentioned in process (a) above, and at a temperature in the range, for example, -30°C to 120°C, conveniently at or near ambient temperature. The compounds of formula VIIIa and VIIIb may, for example, be obtained using a similar procedure to that described in process (a), but employing the appropriately substituted 3-aminobenzenesulphonyl halide or 2-aminobenzenesulphonyl halide.

(d) for a compound of the formula I in which Y is a group of the formula $-CO.NR^7-$, -CO.O- or -CO.S-, a carboxylic acid of the formula IXa or IXb (or a reactive derivative thereof as defined hereinbefore) is reacted with a compound of the formula $R^1.NHR^7$, $R^1.OH$ or $R^1.SH$ respectively. In general the reaction is carried out using conventional conditions for coupling a carboxylic acid with an amine , alcohol or thiol, such as those described under process (c). The compounds of formula IXa and IXb may, for example, be obtained from a compound of the formula 1 in which $-Y-R^1$ is an ester group (for example $-CO.O.CH_3$) by conventional acid or base hydrolysis.

(e) for a compound of the formula I in which R^3 is hydrogen and R^2 is a group $-Y-R^1$ in which Y is a group -CO.O-, -CO.S- or $-CO.NR^7-$, a compound of the formula X is reacted with a compound of the formula $R^1.OH$, $R^1.SH$ or $R^1.NHR^7$ respectively. The reaction is optionally carried out in the presence of a suitable base, for example an alkali metal hydride such as sodium or potassium hydride. The reaction is generally carried out in a suitable inert solvent or diluent as defined hereinbefore and at a temperature in the range, for example, 0°C to 100°C, and conveniently at or about ambient temperature. A compound of formula X in which $\overline{V}$ is nitrogen may be obtained by reaction of a compound of formula $\overline{V}$ with sacharin (or an appropriately substituted sacharin), using similar conditions to those descried for process (b) above. A compound of formula X may also be obtained by cyclisation of a 2-(chlorosulphonyl)benzoyl chloride with an amine of formula III, as illustrated in the Examples.

Whereafter, a compound of the formula I may be converted into another compound of the formula I by conventional functional group interconversion. For example when Y is a group $-CO.NR^7-$ it may be converted to a $-CS.NR^7-$ group by thiation, for example as illustrated in Example 4.

It will be appreciated that it may be necessary to protect one or more functional groups with a suitable protecting group prior to carrying out the process of (a), (b), (c), (d) or (e) above, or prior to carrying out a functional group interconversion, followed by removal of the protecting group. Suitable protecting groups and procedures for their use, together with procedure for removing the protecting group, are well known in the art, for example as described in "Protective Groups in Organic Syntheses" by Theodora Greene (John Wiley and Sons Inc., 1981).

Whereafter, when a pharmaceutically-acceptable salt of a compound of formula I is required, it may be obtained, for example, by reaction with the appropriate base affording a physiologically-acceptable cation, or with the appropriate acid affording a physiologically-acceptable amine, or by any other conventional salt formation procedure.

Further, when an optically active form of a compound of formula I is required, one of the aforesaid processes may be carried out using an optically active starting material. Alternatively, the racemic form of a compound of formula I may be resolved, for example by reaction with a optically active form of a suitable organic base, for example, ephedrine, N,N,N-trimethyl(1-phenylethyl)ammonium hydroxide or 1-phenylethylamine, followed by conventional separation of the diastereoisomeric mixture of salts thus obtained, for example by fractional crystallisation from a suitable solvent, for example a (1-4C)alkanol, whereafter the optically active form of said compound of formula I may be liberated by treatment with acid using a conventional procedure, for example using an aqueous mineral acid such as dilute hydrochloric acid.

As stated above, the compounds of formula I will have beneficial pharmacological effects in warm-blooded animals (including

man) in diseases and medical conditions where elevated or abnormal levels of endothelin play a significant causative role. (References to studies supporting the implication of endothelin in various diseases or medical conditions are, for example, disclosed in International Patent Applications, Publication Nos. WO 93/21219 and WO 94/02474.) The compounds of the invention will thus be useful in the treatment of diseases or medical conditions such as hypertension, pulmonary hypertension, congestive heart failure, dyslipidaemia, atherosclerosis, restenosis, acute and chronic renal failure, ischaemic stroke, subarachnoid haemorrhage, intermittent claudication, critical limb ischaemia, asthma, and organ failure after general surgery or translantation. They may also be useful for the treatment of pre-eclampsia, premature labour, myocardial infarction, angina pectoris, dysrrhythmia, cardiogenic and endotoxin shock, diabetes mellitus, Raynaud's disease, scleroderma, Buerger's disease, systemic sclerosis, bronchitis, acute respiratory distress syndrome, liver cirrhosis, osteoporosis, Crohn's disease, ulcerative colitis, irritable bowel syndrome, urinary incontinence, migraine, glaucoma, arthritis and certain cancers.

The endothelin receptor antagonist activity of the compounds of the invention may be assessed using one or more of the following procedures:

Test A: The endothelin receptor antagonist activity of compounds of formula I may be assessed *in vitro* by their ability to inhibit binding of $[^{125}I]$-Endothelin-1 to its receptors. Human ET_A or ET_B receptors (sub-types of the endothelin receptor) were expressed in Mouse Erythroleukemic Cells (MEL cells) by using standard molecular biology techniques (for example, as described by Sambrook J., Fritsch E.F. & Maniatis T. (1989) Molecular Cloning: A Laboratory Manual, 2nd Edition, Cold Spring Harbor Press, USA). cDNA sequences encoding the human ET_A and ET_B receptor (Hosoda K. et al (1991), FEBS Lett., 287, 23-26 and Sakamoto A. et al, (1991), Biochem. Biophys Res. Comm., 178, 656-663) are subcloned into pBluescript vector followed by insertion into the MEL cell expression vector pEV as described by Needham et al (1992),

Nuc. Acids Res., 20, 997-1003. The resultant expression vector was transfected into MEL cells by electroporation using procedures described by Shelton et al., (1993), Receptors and Channels, 1, 25-37. MEL cells expressing the recombinant human ET_A or ET_B receptor were grown in Dulbecco's Modified Eagle's Medium (DMEM) with 10% Fetal Calf Serum (FCS), 1% glutamine, 1% penicillin/streptomycin and 2 mg/ml Gibco Geneticin (G-418) sulphate. After 3-6 days induction with 1% N,N-dimethylsuphoxide, the MEL cells were harvested for membrane preparation. Freshly prepared MEL cell pellets ($3x10^9$ cells) were homogenised in 30 ml of buffer containing 50mM 2-amino-2-(hydroxymethyl)-1,3-propanediol hydrochloride (Tris HCl), 0.19M sucrose, 5 µg/ml soybean trypsin inhibitor, 100 µg/ml bacitracin, 1mM benzamidine and 1mM phenanthroline pH 7.4 at 5°C. Unbroken cells and nuclei were sedimented by centrifuging the homogenate at 1500 x g for 15 minutes at 5°C. The membrane pellet was resuspended in buffer and stored in liquid nitrogen until use.

$[^{125}I]$-Endothelin-1 binding to MEL cell membranes was measured in incubation buffer containing 50mM Tris HCl, 1mM $CaCl_2$, 0.05% polyoxyethylenesorbitan monolaurate, 0.1% Bovine Serum Albumin (BSA), 0.02% sodium azide pH 7.4 at 30°C after 180 minutes incubation. Membrane suspension (equivalent to 1.5µg and 0.5µg protein/tube ET_A and ET_B receptor respectively) was added to the incubation containing test compound and 30pM$[^{125}I]$-Endothelin-1 in a total volume of 225µl. Nonspecific binding was measured in the presence of 100nM unlabelled Endothelin-1. The incubation was terminated by harvesting the incubation with 50mM Tris pH 7.4 through a GF/B filter on a Brandel cell harvestor. The filter discs were punched out and counted in a gamma counter. Compounds are tested in triplicate over a range of concentrations and IC_{50} values calculated.

In general, compounds of formula I as defined above show inhibition in Test A at a concentration of about 100 micromolar or much less.

Test B: The endothelin receptor antagonist activity of compounds of formula I may be assessed in vitro in isolated tissues by their ability

to inhibit the relaxant response to endothelin-1 in the guinea-pig isolated taenia coli. Guinea pigs of either sex and weight >250 g are killed by cervical dislocation and the caecum removed and placed in cold oxygenated Krebs solution. Strips of taenia coli are dissected out and approximately 4 cm lengths set up for isotonic recording in a 20 ml organ bath containing oxygenated Krebs solution at 32°C. After a 90-120 minute equilibration period to allow the tissue to spontaneously develop an increased tone, a cumulative concentration-response curve (relaxation) is constructed to endothelin-1 (0.3-10nM). The tissue is then washed for a period of at least 90 minutes before construction of a second concentration-response curve to endothelin-1 in the presence of the test compound. The test compound is added to the organ bath (at an initial concentration of 20μM) at least 30 minutes before constructing the second concentration-response curve to endothelin-1. The endothelin-1 concentration ratio for each experiment is determined by comparing the most parallel portions of the control and drug treated concentration-response curves. From this a pA_2 is calculated: pA_2 = -log[molar drug concentration] + log[concentration ratio - 1].

Test C: This *in vivo* test involves the measurement of the antagonist effect of the test compound against the pressor response induced by intravenously-administered proendothelin-1 in a pithed rat preparation.

Male rats (280-330g) are anaesthetised with halothane and artifically respired through a tracheal cannula. Rats are pithed by passing a 2mm diameter needle through the orbit, through the foramen magnum, and down into the spinal canal. The left femoral vein and the right carotid artery are isolated and catheters filled with heparinised saline are implanted for administration of compounds and measurement of blood pressure respectively. Body temperature is maintained at 38°C (as measured rectally) by a heated pad. Rats with an initial baseline mean arterial pressure of less than 55 mmHg or greater than 70 mmHg are excluded. Blood pressure is allowed to stabilize for approximately 10 minutes before a baseline reading is taken. Two initial challenges of proendothelin-1 (0.3 and 1.0 nmol kg^{-1}) are administered intravenously in a cumulative fashion and pressor responses recorded. Thereafter, a

55 minute recovery period is allowed and rats in which the blood pressure fails to return to within 20% of the baseline are excluded. Test compound is dosed intravenously at a dose volume of 1.0 ml kg^{-1} body weight and further challenges of proendothelin-1 are administered 5 minutes later. Proendothelin-1 is administered cumulatively in increasing doses (starting at 0.3 $nmolkg^{-1}$) until pressor responses are observed. Endothelin receptor antagonism is quantified by calculating dose ratio shifts at the 30mmHg change level.

Test D: This *in vivo* test involves the measurement of the antagonist effect of the test compound against the pressor response induced by intravenously-administered proendothelin-1 in a conscious rat preparation.

Male rats (260-290 g) are anaesthetised with Saffan administered via the tail vein. The right jugular vein and carotid artery are isolated and catheters filled with heparin implanted. These are exteriorised at the back of the neck using a metal trochar and the neck incision closed with autoclips. Rats are housed individually with free access to food and water during the recovery phase. Later in the day, food is removed and the rats are fasted overnight with free access to water. The following day the rats are placed in perspex restraining tubes and the arterial catheter drained and connected to a pressure transducer for measurement of mean arterial pressure. Following a ten minute stabilization period, proendothelin-1 (usually 0.3-1.0 nmol kg^{-1}) is administered cumulatively until a pressor response of 30 mmHg is achieved. The animals are then returned to their cages and allowed to recover for 2 hours. The test compound is administered orally (by gavage) at a known time point during the recovery period. The dose response curve to proendothelin-1 is then repeated at a fixed time after the oral dose (usually 0.5 or 1.0 hours) and again at a further time point (3 or 5 hours). Endothelin receptor antagonism is quantified by calculating dose ratio shifts at the 30mmHg change level.

The compounds of formula I will generally be administered for therapeutic or prophylactic purposes to warm-blooded animals (including

man) requiring such treatment in the form of a pharmaceutical composition, as is well known in the pharmaceutical art. According to a further feature of the invention there is provided a pharmaceutical composition comprising a compound of formula I, or a pharmaceutically acceptable salt thereof as defined above, together with a pharmaceutically acceptable diluent or carrier. Such compositions will conveniently be in a form suitable for oral administration (e.g. as a tablet, capsule, solution, suspension or emulsion) or parenteral administration (e.g. as an injectable aqueous or oily solution, or injectable emulsion).

The compounds of formula I, or a pharmaceutically acceptable salt thereof, may also be advantageously administered for therapeutic or prophylactic purposes together with another pharmacological agent known in the general art to be of value in treating one or more of the diseases or medical conditions referred to hereinabove, such as beta-adrenergic blocker (for example atenolol), a calcium channel blocker (for example nifedipine), an angiotensin converting enzyme (ACE) inhibitor (for example lisinopril), a diuretic (for example furosemide or hydrochlorothiazide), an endothelin converting enzyme (ECE) inhibitor (for example phosphoramidon), a neutral endopeptidase (NEP) inhibitor, an HMGCoA reductase inhibitor, a nitric oxide donor, an anti-oxidant, a vasodilator, a dopamine agonist, a neuroprotective agent, a steroid, a beta-agonist, an anti-coagulant, or a thrombolytic agent. It is to be understood that such combination therapy constitutes a further aspect of the invention.

In general a compound of formula I (or a pharmaceutically acceptable salt thereof as appropriate) will be administered to man so that, for example, a daily oral dose of up to 50 mg/kg body weight (and preferably of up to 10 mg/kg) or a daily parenteral dose of up to 5 mg/kg body weight (and preferably of up to 1 mg/kg) is received, given in divided doses as necessary, the precise amount of compound (or salt) administered and the route and form of administration depending on size, age and sex of the person being treated and on the particular disease or medical condition being treated according to principles well

known in the medical arts.

In addition to their aforesaid use in therapeutic medicine in humans, the compounds of formula I are also useful in the veterinary treatment of similar conditions affecting commercially valuable warm-blooded animals, such as dogs, cats, horses and cattle. In general for such treatment, the compounds of the formula I will be administered in an analogous amount and manner to those described above for administration to humans. The compounds of formula I are also of value as pharmacological tools in the development and standardisation of test systems for the evaluation of the effects of endothelin in laboratory animals such as cats, dogs, rabbits, monkeys, rats and mice, as part of the continuing search for new and improved therapeutic agents.

The invention will now be illustrated by the following non-limiting Examples in which, unless otherwise stated:-

(i) concentrations and evaporations were carried out by rotary evaporation _in vacuo_;

(ii) operations were carried out at room temperature, that is in the range 18-26°C;

(iii) flash column chromatography was performed on Merck Kieselgel 60 (Art. no. 9385) obtained from E Merck, Darmstadt, Germany;

(iv) where a silica gel Mega Bond Elut column is referred to, this means a column containing 10g of silica of 40 micron particle size, the silica being contained in a 60 ml disposable syringe and supported by a porous disc, obtained from Varian, Harbor City, California, USA under the name "Mega Bond Elut SI";

(iv) yields, where given, are intended for the assistance of the reader only and are not necessarily the maximum attainable by diligent process development;

(v) ^{1}H NMR spectra were normally determined at 200MHz or 250MHz in $CDCl_3$ or d_6-dimethylsulphoxide (d_6-DMSO) using tetramethylsilane (TMS) as an internal standard, and are expressed as chemical shifts (delta values) in parts per million relative to TMS using conventional

abbreviations for designation of major peaks: s, singlet; m, multiplet; t, triplet; br, broad; d, doublet; and

(vi) HPLC was carried out using a Hypersil ODS 5μ column, available from Shandon HPLC of Runcorn, Cheshire, United Kingdom, employing a flow rate of 1.5 ml/min and a detection wavelength of 280nm, with an oven temperature of 40°C. The eluant was a mixture of a 1 millimolar solution of triethylamine in water (Solvent C) and a 1 millimolar solution of triethylamine in acetonitrile (Solvent D). The eluant was passed through the column as follows: 0-3 minutes, a mixture of Solvent C and Solvent D in the ratio 95:5; 3-17 minutes, a continuous gradient elution starting with a mixture of Solvent C and Solvent D in a ratio of 95:5 and ending with a mixture of Solvent C and Solvent D in a ratio of 5:95. Retention times (t_R) in minutes are given where appropriate.

EXAMPLE 1

Triethylamine (2.5 ml) was added to a solution of 3-(chlorosulphonyl)benzoyl chloride (1.2 g) in dichloromethane (5 ml) at $0^{o}C$ under an atmosphere of argon. The solution was further cooled to -60°C and a solution of tert-butylamine (0.366 g) in dichloromethane (5 ml) was added over 15 minutes. When addition was complete the reaction mixture was stirred a further 2 hours at -60°C and then allowed to warm to 0°C over the next hour. Volatile material was removed by evaporation to give 3-chlorosulphonyl-N-tert-butylbenzamide. Pyridine (5 ml) was added, followed by 2-amino-5-bromo-3-methoxypyrazine (obtained as described in Gazz. Chim. Ital., 1960, 90, 1807) (1.02 g) and 4-pyrrolidinopyridine (0.1 g), and the mixture was heated at 60°C for 18 hours under an atmosphere of argon. Volatile material was removed by evaporation and dichloromethane (50 ml) was added. The solution was washed successively with 2M hydrochloric acid, water and saturated sodium chloride solution and dried ($MgSO_4$). Volatile material was removed by evaporation and the residue was purified by gradient elution through a silica gel Mega Bond Elut column, starting with dichloromethane and increasing to dichloromethane/methanol (19:1 v/v). Trituration of the resultant gum gave 3-[N-(5-bromo-3-methoxypyrazin-2-yl)sulphamoyl]-N-tert-butylbenzamide (0.126 g) as a solid, m.p. 199-202°C; mass spectrum (positive fast atom bombardment (+ve FAB), methanol/m-nitrobenzyl alcohol(NBA)): 443 $(M+H)^+$; NMR ($CDCl_3$): 1.50 (s,9H), 4.03 (s,3H), 5.98 (br s,1H), 7.54-7.70 (m,2H), 7.81 (s,1H), 8.00 (dd,1H), 8.24 (d,1H), 8.40 (s,1H); microanalysis, $C_{16}H_{19}BrN_4O_4S$ requires: C, 43.3; H, 4.3; N, 12.6; found: C, 43.7; H, 4.4; N, 12.3%.

EXAMPLE 2

Sodium hydride (60% dispersion in oil; 0.177 g) was washed with isohexane (3 X 5 ml) and was then suspended in 1,2-dimethoxyethane (DME; 5 ml) and cooled to 5°C under an atmosphere of argon. A solution of 2-amino-5-bromo-3-methoxypyrazine (0.408 g) in DME (5 ml) was added over 25 minutes, maintaining an internal temperature of 5-10°C. After a further 30 minutes a solution of methyl 3-(chlorosulphonyl)benzoate (0.469 g) in DME (3 ml) was added. The reaction mixture was stirred

for 18 hours, cooled and water (10 ml) added. Aqueous 1M citric acid solution was added to acidify the mixture and the mixture was extracted with dichloromethane (4 X 25 ml). The combined extracts were washed with aqueous 2N hydrochloric acid solution, saturated sodium chloride solution and dried ($MgSO_4$). Volatile material was removed by evaporation to give **methyl 3-[_N_-(5-bromo-3-methoxypyrazin-2-yl)-sulphamoyl]benzoate** (0.607 g) as a foam; mass spectrum (+ve FAB, methanol/glycerol(GLY)): 402 $(M+H)^+$; NMR ($CDCl_3$): 3.96 (s,3H), 4.02 (s,3H), 7.55-7.75 (m,2H), 7.82 (s,1H), 8.23-8.42 (m,2H), 8.76 (dd,1H).

The starting material methyl 3-(chlorosulphonyl)benzoate was obtained as follows:

Methanol (6.07 ml) was added to a solution of 3-(chlorosulphonyl)benzoyl chloride (35.85 g) in pyridine (150 ml) under an atmosphere of argon and the mixture was stirred for 2 hours. Volatile material was removed by evaporation and dichloromethane (300 ml) was added. The mixture was washed successively with 1M hydrochloric acid (twice), water and saturated sodium chloride solution, and then dried ($MgSO_4$). Volatile material was removed by evaporation to give methyl 3-(chlorosulphonyl)benzoate (25.0 g) as a solid, m.p. 66-67°C; mass spectrum (positive chemical ionisation (+ve CI)): 137 $(M+H)^+$; NMR ($CDCl_3$): 4.00 (s,3H), 7.74 (t,1H), 8.23 (dd,1H), 8.40 (dd,1H), 8.70 (m,1H).

EXAMPLE 3

1,1-Carbonyldiimidazole (0.089 g) was added to a suspension of 3-[_N_-(5-bromo-3-methoxypyrazin-2-yl)sulphamoyl]benzoic acid (A) (0.194 g) in dichloromethane (3 ml) under an atmosphere of argon. The resultant solution was stirred for 2 hours and 2-(2-methoxyphenyl)-ethylamine (0.073 ml) was added. The reaction mixture was stirred for 18 hours then dichloromethane (10 ml) was added. The reaction mixture was washed successively with 2M hydrochloric acid (twice), water and saturated sodium chloride solution, and then dried ($MgSO_4$). Volatile material was removed by evaporation to give **3-[_N_-(5-bromo-3-methoxypyrazin-2-yl)sulphamoyl]-_N_-[2-(2-methoxyphenyl)ethyl]benzamide**

(0.259 g) as a foam; mass spectrum (+ve FAB, methanol/NBA): 521 $(M+H)^+$; NMR (d_6-DMSO): 2.84 (t,2H), 3.40-3.55 (m,2H), 3.78 (s,3H), 3.98 (s,3H), 6.86 (t,1H), 6.96 (d,1H), 7.06-7.25 (m,2H), 7.66 (t,1H), 7.86 (s,1H), 8.08 (t,2H), 8.41 (s,1H), 8.67-8.80 (br t,1H), 11.22 (br s,1H).

The starting material (A) was obtained as follows:

2M Sodium hydroxide solution (3.75 ml) was added to a solution of methyl 3-[N-(5-bromo-3-methoxypyrazin-2-yl)sulphamoyl]-benzoate (0.6 g) in methanol (5 ml) and the mixture was stirred for 18 hours. Volatile material was removed by evaporation and water (20 ml) was added to the residue. 2M Hydrochloric acid was added to acidify the mixture to pH2 and the solid which precipitated was collected by filtration and washed with water. The solid was dried under vacuum to give 3-[N-(5-bromo-3-methoxypyrazin-2-yl)sulphamoyl]benzoic acid (0.374 g) as a solid, m.p. 239-241°C; mass spectrum (+ve FAB, methanol/DMSO/GLY): 390 $(M+H)^+$; NMR (d_6-DMSO): 3.93 (s,3H), 7.72 (t,1H), 7.89 (s,1H), 8.10-8.27 (m,2H), 8.51 (m,1H), 10.7-11.6 (br s,1H), 12.6-13.90 (br s,1H).

EXAMPLE 4

Lavesson's reagent (2,4-bis(4-methoxyphenyl)-1,3-dithia-2,4-diphosphetane-2,4-disulphide; 0.06 g) was added to a solution of 3-[N-(5-bromo-3-methoxypyrazin-2-yl)sulphamoyl]-N-[2-(2-methoxyphenyl)-ethyl]benzamide (0.129 g) in toluene (3 ml) under an atmosphere of argon. The resultant solution was stirred under reflux for 10 minutes and then cooled to ambient temperature. The reaction mixture was applied directly to a silica gel Mega Bond Elut column. Gradient elution with ethyl acetate/hexane (1:3 to 1:2 v/v) gave 3-[N-(5-bromo-3-methoxypyrazin-2-yl)sulphamoyl-N-[2-(2-methoxyphenyl)ethyl]-thiobenzamide (0.109 g) as a foam; mass spectrum (+ve FAB, methanol/NBA): 537 $(M+H)^+$; NMR (d_6-DMSO): 3.0 (t,2H), 3.8 (s,3H), 3.87 (m,2H), 3.92 (s,3H), 6.9 (m,1H), 7.0 (d,1H), 7.2 (m,2H), 7.6 (t,1H), 7.8 (m,2H), 7.9 (s,1H), 8.05 (m,1H), 10.5 (br t,1H), 11.3 (br s, 1H).

EXAMPLES 5-20

Using a similar procedure to that described in Example 3, but starting from the appropriate amine of formula $R^1.NH_2$ instead of 2-(2-methoxyphenyl)ethylamine, the following compounds of formula IIa, in which A^a = bromo; B^a = methoxy; Y = -CO.NR^7- in which R^7 is hydrogen; and R^4, R^5 and R^6 are all hydrogen, were obtained in yields of 8 - 92%:-

(Example 5): R^1 = 3-methoxyphenethyl; mass spectrum (+ve FAB, methanol/GLY): 521 $(M+H)^+$; NMR ($CDCl_3$): 2.92 (t,2H), 3.67-3.82 (m,2H), 3.80 (s,3H), 4.01 (s,3H), 6.27 (br t,1H), 6.76-6.89 (m,3H), 7.20-7.31 (m,1H), 7.58 (t,1H), 7.75 (s,1H), 7.98 (dd,1H), 8.23 (dd,1H), 8.40 (d,1H); microanalysis, $C_{21}H_{21}BrN_4O_5S$ requires: C, 48.4; H, 4.06; N, 10.7%; found : C, 48.2; H, 4.0; N, 10.5%;

(Example 6): R^1 = 4-methoxyphenethyl; m.p. 173-174°C; mass spectrum (+ve FAB, methanol/NBA): 521 $(M+H)^+$;

(Example 7): R^1 = 2,2-diphenylethyl; mass spectrum (+ve FAB, methanol/GLY) : 567 $(M+H)^+$; NMR ($CDCl_3$): 4.00 (s,3H), 4.10 (m,2H), 4.35 (t,1H), 6.15 (br t,1H), 7.15-7.40 (m,10H), 7.54 (t,1H), 7.64 (s,1H), 7.80-7.90 (m,1H), 8.20 (dd,1H), 8.33 (m,1H);

(Example 8): R^1 = cyclopropyl ; mass spectrum (+ve FAB, methanol/GLY): 427 $(M+H)^+$; t_R = 1.79 minutes;

(Example 9): R^1 = 2-norbornyl; mass spectrum (+ve FAB, methanol/DMSO/GLY): 481 $(M+H)^+$; t_R = 9.0 minutes;

(Example 10): R^1 = cyclohexyl; mass spectrum (+ve FAB, methanol/DMSO/GLY): 469 $(M+H)^+$; t_R = 9.08 minutes;

(Example 11): R^1 = 2-hydroxycyclohexyl; mass spectrum (+ve FAB, methanol/DMSO/GLY): 485 $(M+H)^+$; t_R = 8.64 minutes;

(Example 12): R^1 = cyclohexylmethyl; mass spectrum (+ve FAB,

methanol/GLY): 483 $(M+H)^+$; t_R = 9.24 minutes;

(Example 13): R^1 = 3-(2-oxopyrrolidin-1-yl)propyl; mass spectrum (+ve FAB, methanol/DMSO/GLY): 512 $(M+H)^+$; t_R = 11.35 minutes;

(Example 14): R^1 = tetrahydrofurfuryl; mass spectrum (+ve FAB, methanol/DMSO/GLY): 471 $(M+H)^+$; t_R = 8.31 minutes;

(Example 15): R^1 = 2-oxo-tetrahydro-3-thienyl; mass spectrum (+ve FAB, methanol/GLY): 487 $(M+H)^+$; t_R = 1.84 minutes;

(Example 16): R^1 = 4-fluorophenethyl; mass spectrum (+ve FAB, methanol/DMSO/GLY): 509 $(M+H)^+$; t_R = 9.27 minutes;

(Example 17): R^1 = 4-aminophenethyl; mass spectrum (+ve FAB, methanol/DMSO/GLY): 506 $(M+H)^+$; t_R = 8.72 minutes;

(Example 18): R^1 = nonyl; mass spectrum (+ve FAB, methanol/DMSO/GLY): 513 $(M+H)^+$; t_R = 9.82 minutes;

(Example 19): R^1 = 1-methoxycarbonyl-2-phenylethyl; mass spectrum (+ve FAB, methanol/DMSO/GLY): 549 $(M+H)^+$; t_R = 9.25 minutes; and

(Example 20): R^1 = 9-fluorenyl; mass spectrum (+ve FAB, methanol/DMSO/GLY): 551 $(M+H)^+$; t_R = 9.48 minutes.

EXAMPLE 21

1,1-Carbonyldiimidazole (0.023 g) was added to a suspension of 3-[N-(2-chloro-4-methoxypyrimidin-5-yl)sulphamoyl]benzoic acid (A) (0.037 g) in dichloromethane (5 ml) under an atmosphere of argon. The resultant solution was stirred for 2 hours and phenethylamine (0.014 ml) was added. The reaction mixture was stirred for 18 hours then dichloromethane (10 ml) was added. The reaction mixture was washed successively with 1M hydrochloric acid, water and saturated sodium chloride solution, and then dried ($MgSO_4$). Volatile material was removed by evaporation and the residue was purified by gradient elution

through a silica gel Mega Bond Elut column, starting with hexane/acetic acid (99.9:0.1 v/v) and increasing to ethyl acetate/hexane/acetic acid (50:50:0.1 v/v), to give **3-[N-(2-chloro-4-methoxypyrimidin-5-yl)-sulphamoyl]-N-phenethylbenzamide** (0.020 g) as a gum; mass spectrum (+ve FAB, DMSO/NBA): 447 $(M+H)^+$; NMR (d_6-DMSO): 2.83 (t,2H), 3.50 (m,2H), 3.64 (s,3H), 7.24 (m,5H), 7.63 (t,1H), 7.88 (d,1H), 8.05 (d,1H), 8.20 (d,2H), 8.80 (t,1H).

The starting material (A) was obtained as follows:

(i) 2M Sodium hydroxide solution (1 ml) was added to a solution of methyl 3-[N-(2-chloro-4-methoxypyrimidin-5-yl)sulphamoyl]benzoate (0.16 g) in methanol (5 ml) and the mixture was stirred for 4 hours. Volatile material was removed by evaporation and water (10 ml) was added to the residue. 2M Hydrochloric acid was added to acidify the mixture to pH2 and the solid which precipitated was collected by filtration and washed with water. The solid was dried under vacuum to give 3-[N-(2-chloro-4-methoxypyrimidin-5-yl)sulphamoyl]benzoic acid (0.08 g) as a solid; NMR (d_6-DMSO): 3.66 (s,3H), 7.70 (t,1H), 7.92 (d,1H), 8.18 (d,1H), 8.29 (s,2H); mass spectrum (+ve FAB, methanol/DMSO/NBA): 344 $(M+H)^+$.

EXAMPLE 22

Lithium diisopropylamide (1.5M solution in cyclohexane; 1.85 ml) was added to a solution of 5-amino-2-chloro-4-methoxypyrimidine (0.31 g) in tetrahydrofuran (THF; 15 ml) at -70°C under an atmosphere of argon. The mixture was stirred at -70°C for 15 minutes. A solution of methyl (3-chlorosulphonyl)benzoate (0.501 g) in THF (5 ml) was added at -70°C and the mixture was stirred at -70°C for a further 25 minutes, then at ambient temperature for 1 hour. The mixture was poured into saturated aqueous ammonium chloride solution (20 ml) and extracted with ethyl acetate (4 x 20 ml). The combined extracts were washed successively with water and saturated aqueous sodium chloride solution, and then dried ($MgSO_4$). Volatile material was removed by evaporation and the residue was purified by gradient elution through a silica gel mega Bond Elut column, starting with hexane/acetic acid (99.9:0.1 v/v)

and increasing to ethyl acetate/hexane/acetic acid (40:60:0.1 v/v) to give **methyl 3-[N-(2-chloro-4-methoxypyrimidin-5-yl)sulphamoyl]benzoate** (0.16 g) as a gum; mass spectrum (+ve CI): 358 $(M+H)^+$; NMR (d_6MSO): 3.68 (s,3H), 3.92 (s,3H), 7.72 (t,1H), 7.98 (d,1H), 8.20 (d,1H), 8.30 (d,2H).

The starting material 5-amino-2-chloro-4-methoxypyrimidine was obtained as follows:

A mixture of 5-amino-2,4-dichloropyrimidine (0.32 g) (obtained as described in Chem. Pharm. Bull., (JAPAN), 1958, 6, 343-346) and a solution of sodium methoxide in methanol (from sodium (0.05 g) and methanol (25 ml)) was heated at reflux for 15 minutes and allowed to cool. Volatile material was removed by evaporation and a small volume of water added. The mixture was extracted twice with ether and the combined extracts were dried ($MgSO_4$) and evaporated to give 5-amino-2-chloro-4-methoxypyrimidine (0.2 g) as a solid; mass spectrum (+ve CI): 160 $(M+H)^+$; NMR (d_6-DMSO): 3.92 (s,3H), 5.25 (s,2H), 7.72 (s,1H).

EXAMPLE 23

Using an analogous procedure to that described in Example 21, but using (RS)-1-phenylethylamine (0.013 g) in place of phenethylamine, there was thus obtained **(RS)-3-[N-(2-chloro-4-methoxypyrimidin-5-yl)-sulphamoyl]-N-(1-phenylethyl)benzamide** (0.013 g) as a solid; mass spectrum (+ve FAB, methanol/GLY): 447 $(M+H)^+$; NMR (d_6-DMSO): 1.5 (d,3H), 3.65 (s,3H), 5.18 (q,1H), 7.32 (m,5H), 7.65 (t,1H), 7.88 (d,1H), 8.12 (d,1H), 8.25 (s,2H), 9.03 (d,1H).

EXAMPLE 24

Using an analogous procedure to that described in Example 21, but using 1,1-carbonyldiimidazole (0.049 g), 3-[N-(6-chloropyridazin-3-yl)sulphamoyl]benzoic acid (0.086 g) and phenethylamine (0.038 g), there was thus obtained **3-[N-(6-chloropyridazin-3-yl)sulphamoyl]-N-phenethylbenzamide** as an oil; mass spectrum (+ve FAB, methanol/DMSO/NBA): 417 $(M+H)^+$; NMR (d_6-DMSO): 2.89 (t,2H), 3.55

(t,2H), 7.15-7.35 (m,5H), 7.61-7.78 (m,3H), 8.08 (dd,2H), 8.38(m,1H).

The starting material 3-[N-(6-chloropyridazin-3-yl)-sulphamoyl]benzoic acid was obtained using an analogus procedure to that described in Example 21, part (i) but employing methyl 3-[N-(6-chloropyridazin-3-yl)sulphamoyl]benzoate (0.7 g) and purifiying the product by gradient elution through a silica gel Mega Bond Elut column, starting with hexane/acetic acid (99.9:0.1 v/v) and increasing to ethyl acetate/hexane/acetic acid (50:50:0.1 v/v), to give 3-[N-(6-chloropyridazin-3-yl)sulphamoyl]benzoic acid (0.232 g) as a solid; mass spectrum (+ve FAB, methanol/NBA): 314 $(M+H)^+$; NMR (d_6-DMSO): 7.58-7.78 (br m,3H), 8.15 (m,2H), 8.42 (m,1H).

EXAMPLE 25

Sodium hydride (60% dispersion in mineral oil; 2.12 g) was added to a solution of 3-amino-6-chloropyridazine (3.1 g) in DME (50 ml) at 0°C under an atmosphere of argon. The reaction mixture was stirred for 20 minutes at ambient temperature and methyl 3-(chlorosulphonyl)benzoate (6.2 g) was added. The mixture was stirred at ambient temperature for a further 18 hours. Water (15 ml) was added, followed by aqueous citric acid solution (8% w/v) to acidify the mixture, and the mixture was extracted with ethyl acetate. The combined extracts were washed with saturated sodium chloride solution and then dried ($MgSO_4$). Volatile material was removed by evaporation. The residue was purified by chromatography through a pad of silica gel employing a gradient elution, starting with hexane/acetic acid (99.9:0.1 v/v) and increasing to ethyl acetate/hexane/acetic acid (50:50:0.1 v/v), to give methyl 3-[N-(6-chloropyridazin-3-yl)-sulphamoyl]benzoate (0.7 g) as a gum; mass spectrum (+ve CI): 328 $(M+H)^+$; NMR (d_6-DMSO): 3.90 (s,3H), 7.74-7.82 (br m,3H), 8.16-8.19 (br m,2H), 8.42 (m,1H).

EXAMPLE 26

Using an analogous procedure to that described in Example 24, but using (RS)-1-phenylethylamine in place of phenethylamine, there was thus obtained (RS)-3-[N-(6-chloropyridazin-3-yl)sulphamoyl]-N-

(1-phenylethyl)benzamide (0.01 g) as a solid, m.p. 179-182°C; mass spectrum (+ve FAB, methanol/NBA): 417 $(M+H)^+$; NMR (d_6-DMSO): 1.50(d,3H), 5.18 (m,1H), 7.18-7.42 (m,5H), 7.68 (t,2H), 7.78 (d,1H), 8.05 (d,1H), 8.15 (d,1H), 8.40 (s,1H), 9.06 (d,1H).

EXAMPLE 27

Sodium hydride (60% dispersion in mineral oil; 0.036 g) was added to solution of 2-phenylethanol (0.049 g) in THF (5 ml) at 0°C under an atmosphere of argon. The mixture was warmed to ambient temperature and stirred for 15 minutes. 2-(5-Bromo-3-methoxypyrazin-2-yl)-3-oxo-2,3-dihydro-1,2-benzisothiazole 1,1-dioxide (0.15 g) was added and the mixture was stirred at ambient temperature for 2 hours. Water (5 ml) was added and the mixture was extracted with ethyl acetate. The combined extracts were washed with saturated sodium chloride solution and then dried ($MgSO_4$). Volatile material was removed by evaporation and the residue was purified by gradient elution through a silica gel Mega Bond Elut column, starting with hexane/acetic acid (99.9:0.1 v/v) and increasing to ethyl acetate/hexane/acetic acid (20:80:0.1 v/v) to give **phenethyl 2-[N-(5-bromo-3-methoxypyrazin-2-yl)-sulphamoyl]benzoate** (0.027 g) as a solid; mass spectrum (+ve FAB, DMSO/methanol/NBA): 492 $(M+H)^+$; NMR (d_6-DMSO): 3.00 (t,2H), 3.90 (s,3H), 4.46 (t,2H), 7.27 (m,5H), 7.57 (m,1H), 7.70 (m,2H), 7.85 (s,1H), 8.03 (m,1H).

EXAMPLE 28

4-Pyrrolidinopyridine (0.005 g) was added to a solution of methyl 2-(chlorosulphonyl)benzoate (4.68 g) and 2-amino-5-bromo-3-methoxypyrazine (4.04 g) in pyridine (50 ml). The mixture was stirred at 0°C for 20 minutes and then at 100°C for 6 hours. Volatile material was removed by evaporation. The residue was dissolved in dichloromethane (250 ml) and the solution was washed with 2M hydrochloric acid and dried ($MgSO_4$). Volatile material was removed by evaporation and the residue was purified by chromatography through a pad of silica gel employing gradient elution, starting with hexane/acetic acid (99.9:0.1 v/v) and increasing to ethyl acetate/hexane/acetic acid (30:70:0.1 v/v), to give **methyl**

2-[N-(5-bromo-3-methoxypyrazin-2-yl)sulphamoyl]benzoate (0.856 g) as a solid; mass spectrum (+ve FAB, methanol/NBA): 402 $(M+H)^+$; NMR (d_6-DMSO): 3.82 (s,3H), 3.92 (s,3H), 7.71 (br m,3H), 7.89 (s,1H), 8.08 (m,1H).

EXAMPLE 29

Phenethylamine (0.05 g) was added to a solution of 2-(5-bromo-3-methoxypyrazin-2-yl)-3-oxo-2,3-dihydro-1,2-benzisothiazole 1,1-dioxide (0.15 g) in toluene (10 ml) and the mixture was heated under reflux for 5 hours. Volatile material was removed by evaporation. The residue was purified by gradient elution through a silica gel Mega Bond Elut column, starting with hexane/acetic acid (99.9:0.1 v/v) and increasing to ethyl acetate/hexane/acetic acid (40:60:0.1 v/v), to give **2-[N-(5-bromo-3-methoxypyrazin-2-yl)sulphamoyl]-N-phenethylbenzamide** (0.14 g), as a solid; mass spectrum (+ve FAB, methanol/NBA): 491 $(M+H)^+$; NMR (d_6-DMSO): 2.86 (t,2H), 3.50 (q,2H), 3.92 (s,3H), 7.15-7.35 (br m,5H), 7.45 (d,1H), 7.65 (m,2H), 7.89 (s,1H), 8.05 (d,2H), 8.75 (t,1H); microanalysis, $C_{20}H_{19}BrN_4O_4S$ (+ 0.75 CH_3CO_2H) requires: C, 48.1; H, 4.13; N, 10.4%; found : C, 48.5; H, 4.3; N, 10.1%.

EXAMPLE 30

A solution of phenethylamine (0.04 g) in toluene (0.5 ml) was added to a solution of 2-(6-chloropyridazin-3-yl)-3-oxo-2,3-dihydro-1,2-benzisothiazole 1,1-dioxide (0.097 g) in toluene (1.5 ml) and the reaction mixture was stirred for 18 hours. Solvent was removed by evaporation to give a yellow gum, which was crystallised from hot toluene to give **2-[N-(6-chloropyridazin-3-yl)sulphamoyl]-N-phenethylbenzamide** as a yellow crystalline solid (0.025 g), m.p. 80-82°C; mass spectrum (+ve CI): 417 $(M+H)^+$.

The starting material 2-(6-chloropyridazin-3-yl)-3-oxo-2,3-dihydro-1,2-benzisothiazole 1,1-dioxide was obtained as follows:

A solution of saccharin (1.83 g) in DMF (5 ml) was added slowly to a stirred suspension of sodium hydride (0.24 g; washed free of mineral oil with hexane). Addition caused evolution of a gas and

resulted in a clear solution which was stirred for 10 minutes. A solution of 3,6-dichloropyridazine (1.49 g) in DMF (5 ml) was added dropwise to give a dark yellow solution. The reaction mixture was heated under reflux for 2 hours, then cooled to ambient temperature and poured into water (50 ml). The solid which precipitated was collected by filtration and dried under vacuum to give 2-(6-chloropyridazin-3-yl)-3-oxo-2,3-dihydro-1,2-benzisothiazole 1,1-dioxide (0.51 g), m.p. 236-238°C; mass spectrum (+ve CI): 296 $(M+H)^+$.

EXAMPLE 31

Using an analogous procedure to that described in Example 30, but starting from isopropylamine (0.02 g) instead of phenethylamine, there was thus obtained **N-isopropyl-2-[N-(6-chloropyridazin-3-yl)-sulphamoyl]benzamide** (0.025 g), m.p. 148-150°C; mass spectrum (+ve CI): 355 $(M+H)^+$.

EXAMPLE 32

Using an analogous procedure to that described in Example 30, but starting from (RS)-1-phenylethylamine (0.04 g) and heating the reaction mixture to reflux for 1 hour before stirring at ambient temperature for 18 hours, there was thus obtained **(RS)-2-[N-(6-chloropyridazin-3-yl)sulphamoyl]-N-(1-phenylethyl)-benzamide** (0.075 g), m.p. 82-84°C; mass spectrum (+ve CI): 417 $(M+H)^+$.

EXAMPLE 33

Using an analogous procedure to that described in Example 30, but starting from aniline (0.031 g) and heating the reaction mixture to reflux for 1 hour before stirring at ambient temperature for 18 hours, there was thus obtained **2-[N-(6-chloropyridazin-3-yl)sulphamoyl)-N-phenylbenzamide** (0.046 g), m.p. 75-77°C; mass spectrum (+ve CI): 389 $(M+H)^+$.

EXAMPLE 34

Sodium hydride (60% dispersion in mineral oil; 0.024 g) was added to a solution of benzyl alcohol (0.054 g) in THF (4 ml) and

stirred for 15 minutes. N-(5-Bromo-3-methoxypyrazin-2-yl)-3-oxo-2,3-dihydro-1,2-benzisothiazole 1,1-dioxide (0.185 g) was added in a single portion and the reaction allowed to stir for 18 hours. The solid which precipitated was collected by filtration and washed with diethyl ether (2 x 5 ml) to give **benzyl 2-[N-(5-bromo-3-methoxypyrazin-2-yl)-sulphamoyl]benzoate**, sodium salt (0.194 g); mass spectrum (+ve FAB, (DMSO/NBA): 477 $(M+H)^+$ (for free acid); NMR (d_6-DMSO, 250 MHz): 7.95 (dd,1H), 7.49-7.25 (m,9H), 5.16 (s,2H), 3.74 (s,3H).

The starting material N-(5-bromo-3-methoxypyrazin-2-yl)-3-oxo-2,3-dihydro-1,2-benzisothiazole 1,1-dioxide was obtained as follows:

(i) Sodium hydride (60% dispersion in mineral oil; 5.0 g) was added portionwise to a stirred solution of 2-amino-5-bromo-3-methoxypyrazine (10.2 g) in DME (100 ml) causing a colour change from pale yellow to dark green. After 15 minutes a solution of 2-(chlorosulphonyl)benzoyl chloride (prepared as described in J. Org. Chem. 1962, 27, 1703-1709) (11.9 g) in DME (20 ml) was added dropwise over 5 minutes. The reaction mixture was allowed to stir for a further 18 hours. 1M Hydrochloric acid (100 ml) was added, followed by dichloromethane (250 ml). The organic layer was separated, the aqueous phase was extracted with dichloromethane (2 x 150 ml) and the combined organic layers were dried ($MgSO_4$). Solvent was removed by evaporation to give a solid, which was purified by chromatography on silica gel, eluting with dichloromethane, to give N-(5-bromo-3-methoxypyrazin-2-yl)-3-oxo-2,3-dihydro-1,2-benzisothiazole 1,1-dioxide as a pale cream solid, (9.25 g), m.p. 216-217°C; mass spectrum (+ve CI): 370 $(M+H)^+$.

EXAMPLES 35-43

Using an analogous procedure to that described in Example 34, but starting from the appropriate alcohol of formula $R^1.OH$ instead of benzyl alcohol, the following compounds of formula IId in which A^a = bromo; B^a = methoxy; Y = -CO.O- and R^4, R^5 and R^6 are all hydrogen, were obtained in the form of their sodium salts in yields of 13 to 90%:-

(Example 35): R^1 = 4-Phenylbenzyl; mass spectrum (+ve FAB, DMSO/NBA): 554 $(M+H)^+$ (for free acid); NMR (d_6-DMSO, 200 MHz): 7.97 (dd,1H), 7.69-7.61 (m,2H), 7.57 (s,3H), 7.54-7.36 (m,6H), 7.34 (s,1H), 7.31 (dd,1H), 5.21 (s,2H), 3.74 (s,3H);

(Example 36): R^1 = 2-Benzylbenzyl; mass spectrum (+ve FAB, DMSO/NBA): 568 $(M+H)^+$ (for free acid); NMR (d_6-DMSO, 200 MHz): 7.93 (d,1H), 7.49-7.36 (m,3H), 7.31-7.26 (m,3H), 7.25 (s,1H), 7.23-7.15 (m,6H), 5.16 (s,2H), 4.11 (s,2H), 3.68 (s,3H);

(Example 37): R^1 = 4-Methoxybenzyl; mass spectrum (+ve FAB, DMSO/NBA): 508 $(M+H)^+$ (for free acid); NMR (d_6-DMSO, 250 MHz): 7.92 (dd,1H), 7.43 (m,2H), 7.30-7.18 (m,2H), 7.29 (s,1H), 7.13 (m,1H), 7.00 (d,1H), 6.83 (dd,1H), 5.15 (s,2H), 3.75 (s,3H), 3.74 (s,3H);

(Example 38): R^1 = 2-Naphthylmethyl; mass spectrum (+ve FAB, DMSO/NBA): 528 $(M+H)^+$ (for free acid); NMR (d_6-DMSO, 200 MHz): 7.98-7.83 (m,5H), 7.66 (dd,1H), 7.51-7.37 (m,4H), 7.31 (m,1H), 7.32 (s,1H), 5.35 (s,2H), 3.73 (s,3H);

(Example 39): R^1 = 2-Bromobenzyl; mass spectrum (+ve FAB, DMSO/NBA): 558 $(M+H)^+$ (for free acid); NMR (d_6-DMSO, 250 MHz): 7.96 (d,1H), 7.60 (m,2H), 7.53-7.40 (m,2H), 7.37-7.20 (m,3H), 7.30 (s,1H), 5.23 (s,2H), 3.72 (s,3H);

(Example 40): R^1 = 2,4-Difluorobenzyl; mass spectrum (+ve FAB, DMSO/NBA) : 514 $(M+H)^+$ (for free acid); NMR (d_6-DMSO, 250 MHz); 7.96 (d,1H), 7.75 (q,1H), 7.51-7.38 (m,2H), 7.30-7.18 (m,2H), 7.28 (s,1H), 7.00 (m,1H), 5.20 (s,2H), 3.74 (s,3H);

(Example 41): R^1 = 3-Chlorobenzyl; mass spectrum (+ve FAB, DMSO/NBA): 512 $(M+H)^+$ (for free acid); NMR (d_6-DMSO, 250 MHz); 7.95 (d,1H), 7.56 (br s,1H), 7.51-7.28 (m,7H), 5.19 (s,2H), 3.74 (s,3H);

Example 42: R^1 = 4-Bromobenzyl; mass spectrum (+ve FAB, DMSO/NBA): 556

(M+H)$^+$ (for free acid); NMR (d_6-DMSO, 250 MHz); 7.97 (d,1H), 7.50-7.38 (m,6H), 7.32-7.28 (m,2H), 5.15 (s,2H), 3.73 (s,3H); and

(Example 43): R^1 = **4-Methylthiobenzyl;** mass spectrum (+ve FAB, DMSO/NBA): 524 (M+H)$^+$ (for free acid); NMR (d_6-DMSO, 250 MHz); 7.95 (d,1H), 7.50-7.38 (m,4H), 7.31 (s,1H), 7.28 (m,1H), 7.18 (d,2H), 5.13 (s,2H), 3.74 (s,3H), 2.48 (s,3H).

EXAMPLE 44

Using an analogous procedure to that described in Example 34, but starting with 3,4-dimethylbenzyl alcohol and working the reaction up by addition of 1M hydrochloric acid, followed by chromatography on silica gel eluting with dichloromethane, there was thus obtained **3,4-dimethylbenzyl 2-[N-(5-bromo-3-methoxypyrazin-2-yl)sulphamoyl]-benzoate** in 17% yield, m.p. 121-122°C; mass spectrum (+ve FAB, DMSO/NBA): 506 (M+H)$^+$.

EXAMPLE 45

Sodium hydride (60% dispersion in mineral oil; 0.048 g)) was added to a solution of 4-methylbenzylamine (0.121 g) in THF (4 ml). After 15 minutes N-(5-bromo-3-methoxypyrazin-2-yl)-3-oxo-2,3-dihydro-1,2-benzisothiazole 1,1-dioxide (0.37 g) was added in a single portion and the reaction mixture was allowed to stir for 18 hours. The solid which precipitated was collected by filtration and washed with diethyl ether (2 x 5 ml) to give **2-[N-(5-bromo-3-methoxypyrazin-2-yl)-sulphamoyl]-N-(4-methylbenzyl)benzamide, sodium salt** (0.363 g); mass spectrum (+ve FAB, DMSO/NBA): 491 (M+H)$^+$ (for free acid); NMR (d_6-DMSO, 250 MHz); 9.88 (t,1H), 7.87 (m,1H), 7.53 (m,1H), 7.43 (m,2H), 7.19 (d,2H), 7.08 (s,1H), 7.00 (d,2H), 4.34 (d,2H), 3.53 (s,3H), 2.27 (s,3H).

EXAMPLE 46

A solution of phenethylamine (0.06 g) in toluene (0.5 ml) was added to a solution of N-(2-chloro-4-methoxypyrimidin-5-yl)-3-oxo-2,3-dihydro-1,2-benzisothiazole 1,1-dioxide (A) (0.163 g) in toluene (3 ml). The reaction mixture was heated to reflux and then allowed to

stir for 48 hours at ambient temperature. The solid which precipitated was collected by filtration to give **2-[N-(2-chloro-4-methoxypyrimidin-5-yl)sulphamoyl]-N-(phenethyl)benzamide** as a white solid (0.105 g), m.p. 138-139°C; mass spectrum (+ve FAB, NBA/DMSO): 447 $(M+H)^+$.

The starting material (A) was prepared using an analogous procedure to that described in Example 34, part (i), but employing 5-amino-2-chloro-4-methoxypyrimidine. N-(2-chloro-4-methoxypyrimidin-5-yl)-3-oxo-2,3-dihydro-1,2-benzisothiazole 1,1-dioxide was obtained as a white solid (2.45 g), m.p. 193-194°C; mass spectrum (+ve CI): 326 $(M+H)^+$.

EXAMPLES 47-48

Using an analogous procedure to that described in Example 46 but starting from the appropriate amine of formula $R^1.NH_2$, the following compounds of formula IIe in which A^b = chloro; B^b = methoxy; Y = $-CO.NR^7-$ in which R^7 is hydrogen, and R^4, R^5 and R^6 are all hydrogen, were obtained in yields of 47 to 73%:-

(Example 47): R^1 = Isopropyl; m.p. 154-155°C; mass spectrum (+ve FAB, NBA/DMSO): 385 $(M+H)^+$; and

(Example 48): R^1 = 1-Phenylethyl; m.p. 84-86°C; mass spectrum (+ve FAB, NBA/DMSO): 447 $(M+H)^+$.

EXAMPLE 49

2-Phenylethanol (0.061 g) was added to a stirred suspension of sodium hydride (60% dispersion in mineral oil; 0.05 g) in DMF (3 ml). After 5 minutes a solution of N-(2-chloro-4-methoxypyrimidin-5-yl)-3-oxo-2,3-dihydro-1,2-benzisothiazole 1,1-dioxide (0.163 g) was added and the reaction mixture was heated to reflux and then allowed to stir for 48 hours at ambient temperature. The solid which precipitated was collected by filtration and washed with diethyl ether (2 x 5 ml) to give **phenethyl 2-[N-(2-chloro-4-methoxypyrimidin-5-yl)sulphamoyl]-benzoate, sodium salt** as a white solid (0.18 g), m.p. 133-135°C; mass spectrum (+ve FAB, NBA/DMSO): 448 $(M+H)^+$.

EXAMPLE 50

Using an analogous procedure to that described in Example 49, but using benzyl alcohol in place of 2-phenylethanol, there was thus obtained **benzyl 2-[N-(2-chloro-4-methoxypyrimidin-5-yl)sulphamoyl]-benzoate** in 43% yield, m.p. 145-147°C; mass spectrum (+ve FAB, NBA/DMSO): 434 $(M+H)^+$.

EXAMPLE 51

Pyridine (0.020 ml) was added to a solution of 3-amino-N-(5-bromo-3-methoxypyrazin-2-yl)benzenesulphonamide (A) (0.058 g) in dichloromethane (4 ml), followed by phenylpropionyl chloride (0.030 ml), and the resultant solution was stirred for 4 hours under an atmosphere of argon. The reaction mixture was applied directly to a silica gel Mega Bond Elut column. Gradient elution with ethyl acetate/hexane (1:3 to 1:1 v/v) gave **N-[3-(N-[5-bromo-3-methoxypyrazin-2-yl]sulphamoyl)phenyl]-3-phenylpropionamide** (0.054 g) as a foam; mass spectrum (+ve FAB, methanol/NBA): 490 $(M+H)^+$; NMR (d_6-DMSO): 2.65 (t,2H), 2.93 (t,2H), 3.9 (s,3H), 7.1-7.3 (m,5H), 7.5 (t,1H), 7.6 (m,1H), 7.8 (m,1H), 7.9 (s,1H), 8.3 (t,1H), 10.2 (s,1H), 11.2 (br s,1H).

The starting material (A) was obtained as follows:

Sodium hydride (60% dispersion in oil; 0.28 g) was washed with hexane (3 x 10 ml) under an atmosphere of argon and DME (2 ml) was added with stirring. A solution of 2-amino-5-bromo-3-methoxypyrazine (0.653 g) in DME (8 ml) was added to the suspension. After effervescence ceased, a solution of 3-aminophenylsulphonyl fluoride (0.63 g) in DME (6 ml) was added cautiously. The reaction mixture was stirred for 18 hours and then poured into 2M hydrochloric acid. The mixture was extracted with ethyl acetate and the solvent was then removed by evaporation to give a solid. The solid was dissolved in 2M aqueous sodium hydroxide solution and the solution was washed with dichloromethane. The washings were discarded and the aqueous phase was acidified with potassium hydrogen sulphate solution. The acidic solution was extracted exhaustively with dichloromethane and the combined extracts were washed with saturated sodium chloride solution

and dried ($MgSO_4$). Volatile material was removed by evaporation to give 3-amino-N-(5-bromo-3-methoxypyrazin-2-yl)-benzenesulphonamide (0.20 g) as a solid, m.p. 204-207°C; mass spectrum (+ve CI): 359 $(M+H)^+$.

EXAMPLE 52

Using an analogous procedure to that described in Example 2, but employing 2,5-dimethoxybenzenesulphonyl chloride instead of methyl 3-(chlorosulphonyl)benzoate, there was thus obtained 3-[N-(5-bromo-3-methoxypyrazin-2-yl)sulphamoyl]-2,5-dimethoxybenzenesulphonamide (in 25% yield), m.p. 207-208°C; mass spectrum (+ve CI): 404 $(M+H)^+$.

EXAMPLE 53

2-Amino-5-bromo-3-methoxypyrazine (0.48 g) was added to a stirred suspension of sodium hydride (60% dispersion in oil; 0.24 g) in DME (5 ml). When evolution of gas ceased, 2,5-diethylbenzenesulphonyl chloride (0.5 g) was added and the reaction mixture was stirred for 18 hours under an atmosphere of nitrogen. The reaction mixture was then poured into water (100 ml) and acidified with concentrated hydrochloric acid to adjust the mixture to pH2. The mixture was extracted with ethyl acetate (3 x 150 ml) and the combined extracts were dried ($MgSO_4$) and evaporated to give an oil. The oil was purified by flash chromatography, eluting with dichloromethane/methanol/6M methanolic ammonia solution (98:1:1 v/v) to give N-(5-bromo-3-methoxypyrazin-2-yl)-2,5-diethylbenzenesulphonamide, m.p. 122-124°C; mass spectrum (+ve FAB, methanol/NBA): 400 $(M+H)^+$; NMR (d_6-DMSO, 250 MHz):1.14 (d,3H), 1.18 (d,3H), 2.55 (q,2H), 3.02 (q,2H), 3.90 (s,3H), 7.30 (d,1H), 7.40 (d,1H), 7.81 (m,2H), 11.2 (s,1H).

EXAMPLE 54

Using an analogous procedure to that described in Example 2, but using sodium hydride (0.24 g), 2-amino-5-bromo-3-methoxypyrazine (0.408 g) and 2-benzylbenzenesulphonyl chloride (0.532 g), there was thus obtained N-(5-bromo-3-methoxypyrazin-2-yl)-2-benzylbenzenesulphonamide (0.082g) as a solid; m.p. 204-206°C; mass spectrum

(+ve FAB, methanol/DMSO/MDC/GLY): 436$(M+H)^+$.

The starting material was obtained as follows:

i) A solution of sodium nitrite (3.7 g) in water (5.4 ml) was added dropwise to a solution of 2-benzylaniline (9.15 g) in a mixture of glacial acetic acid (5 ml) and concentrated aqueous hydrochloric acid (11.7 ml) at such a rate as to keep the reaction temperature between -8°C and -10°C. The reaction was stirred for 20 minutes at -10°C after addition had been completed and was then added to a solution of sulphur dioxide and copper (I) chloride in acetic acid at 14°C (this solution had been prepared by bubbling sulphur dioxide through acetic acid (50 ml) for 20 minutes and then adding copper (I) chloride (1.25g) before continuing to add sulphur dioxide for a further 20 minutes). The mixture was allowed to warm to ambient temperature and stir for a further 30 minutes before addition of ice/water (170 ml). The aqueous was extracted with diethyl ether (3 x 200 ml) and the combined organic layers were washed with saturated aqueous sodium bicarbonate solution (3 x 150 ml), dried ($MgSO_4$) and evaporated in vacuo to give a brown oil. This was purified by flash chromatography on silica gel, eluting with isohexane, to give 2-benzylbenzenesulphonyl chloride as a pale red oil (1.40 g) ; mass spectrum (+ve CI): 266 $(M)^+$; NMR (d_6-DMSO): 4.58 (s,2H), 7.19-7.38 (m,6H), 7.43 (m,1H), 7.58 (m,1H), 8.14 (d,1H).

EXAMPLE 55

Using an analogous procedure to that described in Example 2, but using sodium hydride (0.24 g), 2-amino-5-bromo-3-methoxypyrazine (0.408 g) and 2-benzoylbenzenesulphonyl chloride (0.561 g), there was thus obtained **N-(5-bromo-3-methoxypyrazin-2-yl)-2-benzoylbenzenesulphonamide** (0.113 g) as a solid; m.p. 208-210°C; mass spectrum (+ve FAB, methanol/NBA): 448 $(M+H)^+$.

The starting material, 2-benzoylbenzenesulphonyl chloride, was obtained using an analogous procedure to that described in Example 54, part (i), but employing 2-aminobenzophenone (9.85 g), to give 2-benzoylbenzenesulphonyl chloride (1.87 g) as a solid; mass spectrum

(+ve CI): 281 $(M+H)^+$; NMR (d_6-DMSO): 7.43 (m,3H), 7.60 (m,1H), 7.77 (m,4H), 8.20 (d,1H).

EXAMPLE 56

Using an analogous procedure to that described in Example 2, but using sodium hydride (0.24 g), 2-amino-5-bromo-3-methoxypyrazine (0.408 g) and 2-phenoxybenzenesulphonyl chloride (0.537g), there was thus obtained **N-(5-bromo-3-methoxypyrazin-2-yl)-2-phenoxy-benzenesulphonamide** (0.038 g) as a solid; m.p. 179-180°C; mass spectrum (+ve FAB, methanol/NBA): 436 $(M+H)^+$.

The starting material, 2-phenoxybenzenesulphonyl chloride, was obtained using an analogous procedure to that described in Example 54, part (i), but employing 2-phenoxyaniline (9.85 g), to give 2-phenoxybenzenesulphonyl chloride (1.13 g) as an oil; mass spectrum (+ve EI (positive electron impact)): 268 $(M)^+$; NMR (d_6-DMSO): 6.94 (d,1H), 7.16 (m,2H), 7.24 (m,2H), 7.42 (t,2H), 7.57 (t,1H), 8.03 (d,1H).

EXAMPLE 57

Using an analogous procedure to that described in Example 2, but using sodium hydride (0.24 g), 2-amino-5-bromo-3-methoxypyrazine (0.408 g) and 2-(phenylsulphonyl)benzenesulphonyl chloride (0.633 g), there was thus obtained **N-(5-bromo-3-methoxypyrazin-2-yl)-2-(phenylsulphonyl)benzenesulphonamide** (0.047 g) as a solid; m.p. 186-188°C; mass spectrum (+ve FAB, DMSO/NBA): 486$(M+H)^+$.

The starting material, 2-(phenylsulphonyl)benzenesulphonyl chloride, was obtained using an analogous procedure to that described in Example 54, part (i), but employing 2-(phenylsulphonyl)aniline (9.85 g), to give 2-(phenylsulphonyl)benzenesulphonyl chloride (9.31 g) as a solid; m.p. 123-125°C; mass spectrum (+ve CI): 334 $(M+NH_4)^+$.

EXAMPLE 58

Using an analogous procedure to that described in Example 2, but using sodium hydride (0.12 g), 2-amino-5-bromo-3-methoxypyrazine

(0.204 g) and 5-chloro-2-(4-chlorophenylthio)benzenesulphonyl chloride (0.354 g), there was thus obtained **N-(5-bromo-3-methoxypyrazin-2-yl)-5-chloro-2-(4-chlorophenylthio)benzenesulphonamide** (0.167 g) as a solid; mass spectrum (+ve FAB, methanol/DMSO/GLY): 524 $(M+H)^+$; NMR (d_6-DMSO): 4.04 (s,3H), 7.30 (d,1H), 7.45 (d,2H), 7.61 (d,2H), 7.79 (dd,1H), 8.06 (s,1H), 8.21 (d,1H).

The starting material, 5-chloro-2-(4-chlorophenylthio)-benzenesulphonyl chloride, was obtained using an analogous procedure to that described in Example 54, part (i), but employing 5-chloro-2-(4-chlorophenylthio)aniline (3.23 g), to give 5-chloro-2-(4-chlorophenylthio)benzenesulphonyl chloride (0.575 g) as a solid; mass spectrum (+ve CI): 352$(M+H)^+$; NMR (d_6-DMSO): 6.98 (d,1H), 7.45 (m,5H), 8.09 (d,1H).

EXAMPLE 59

Using an analogous procedure to that described in Example 2, but using sodium hydride (0.10 g), 2-amino-5-bromo-3-methoxypyrazine (0.139 g) and 2-anilino-5-nitrobenzenesulphonyl chloride (0.327 g), there was thus obtained **2-anilino-N-(5-bromo-3-methoxypyrazin-2-yl)-5-nitrobenzenesulphonamide** (0.038 g) as a solid; m.p. 95-97°C; mass spectrum (+ve FAB, methanol/NBA): 416 $(M+H)^+$.

The starting material was obtained as follows:

i) Aniline (60 g), calcium carbonate (30 g) and sodium 2-chloro-5-nitrobenzenesulphonate (129.8 g) were heated under reflux in water (500 ml) for 68 hours. The hot reaction mixture was filtered and the filtrate allowed to cool to ambient temperature. The solid which precipitated was collected by filtration, washed with cold water (50 ml) and dried in vacuo to give sodium 2-anilino-5-nitro-benzenesulphonate as a solid (115.4 g); m.p. 250-252°C; mass spectrum (-ve FAB, methanol/GLY): 293 (M-H)-.

ii) Sodium 2-anilino-5-nitrobenenesulphonate (0.948 g) was added to a solution of phosphorus pentachloride (0.626 g) in dichloromethane (10 ml). The reaction mixture was stirred at ambient temperature for 18 hours and then heated at reflux for 15 minutes. The insoluble solid

was filtered off and the filtrate evaporated down to a brown oil. The recovered solid was resubjected to the reaction conditions three times, after which time the four product oils so obtained were combined. The combined oils were taken up in dichloromethane (10 ml) and the solution was washed (2 x 5 ml water, followed by 5 ml dilute aqueous sodium bicarbonate solution), dried ($MgSO_4$) and then evaporated in vacuo to give 2-anilino-5-nitrobenzenesulphonyl chloride as an oil (0.386 g); mass spectrum (+ve CI): 312 $(M)^+$; NMR(d_6-DMSO): 7.10 (d,1H), 7.20-7.50 (m,5H), 8.20 (m,2H), 8.85 (d,1H).

<u>EXAMPLE 60</u> (<u>Note</u>: all parts by weight)

The compounds of the invention may be administered for therapeutic or prophylactic use to warm-blooded animals such as man in the form of conventional pharmaceutical compositions, typical examples of which include the following:-

a) <u>Capsule</u> (for oral administration)

Active ingredient *	20
Lactose powder	578.5
Magnesium stearate	1.5

b) <u>Tablet</u> (for oral administration)

Active ingredient *	50
Microcrystalline cellulose	400
Starch (pregelatinised)	47.5
Magnesium stearate	2.5

c) <u>Injectable Solution</u> (for intravenous administration)

Active ingredient *	0.05 - 1.0
Propylene glycol	5.0
Polyethylene glycol (300)	3.0 - 5.0
Purified water	to 100%

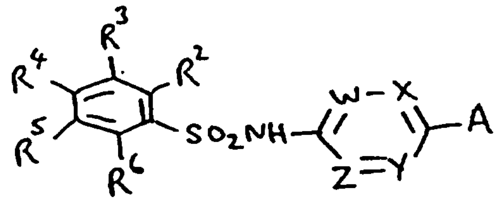
d) <u>Injectable Suspension</u> (for intramuscular administration)

Active ingredient *	0.05 - 1.0
Methylcellulose	0.5
Tween 80	0.05
Benzyl alcohol	0.9
Benzalkonium chloride	0.1
Purified water	to 100%

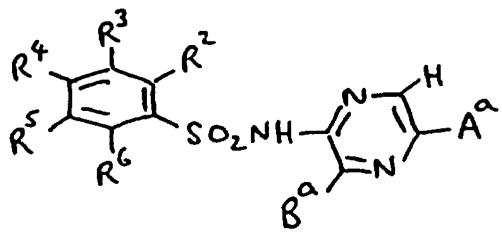
<u>Note</u>: the active ingredient * may typically be an Example described hereinbefore or as a pharmaceutically acceptable salt. Tablets and capsules formulations may be coated in conventional manner in order to modify or sustain dissolution of the active ingredient. Thus, for example, they may be coated with a conventional enterically digestible coating.

HS70020
JJH 25OCT95

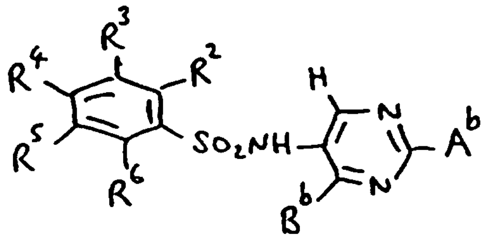
Chemical Formulae



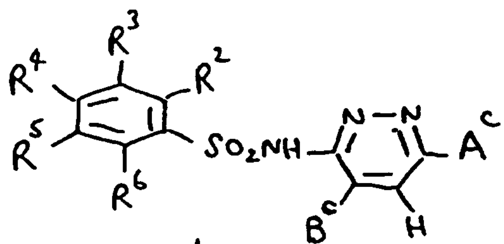
I



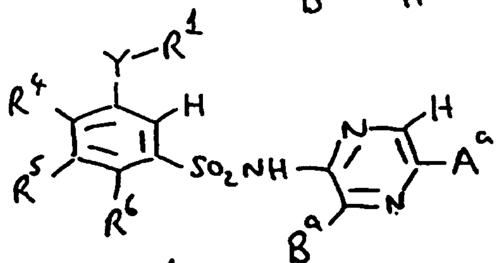
Ia



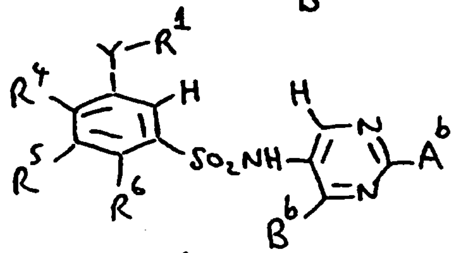
Ib



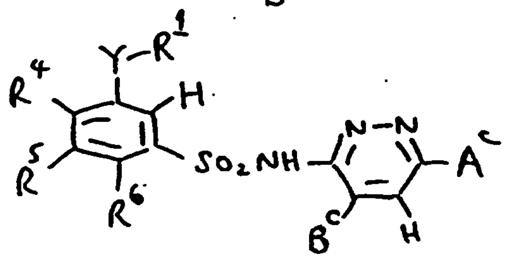
Ic



IIa

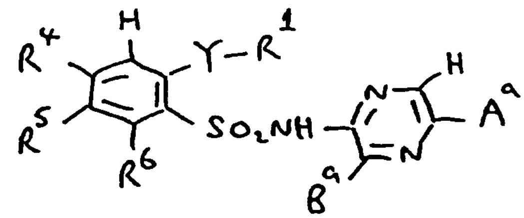


IIb

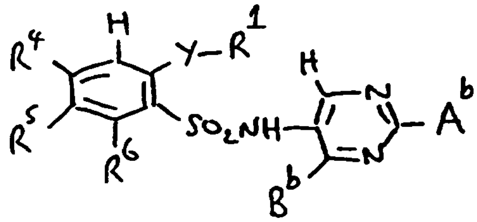


IIc

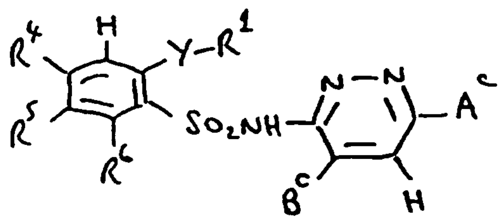
Chemical Formulae
(continued)



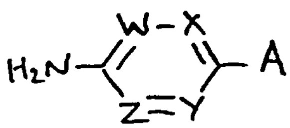
IId



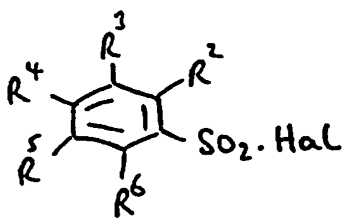
IIe



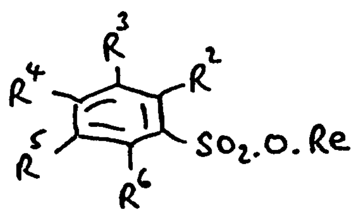
IIf



III



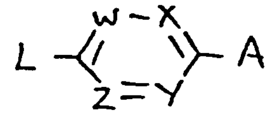
IV



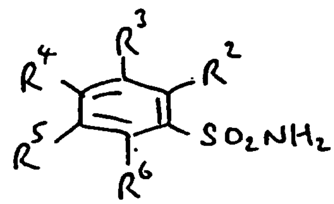
IVa

Chemical Formulae

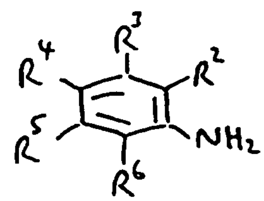
(continued)



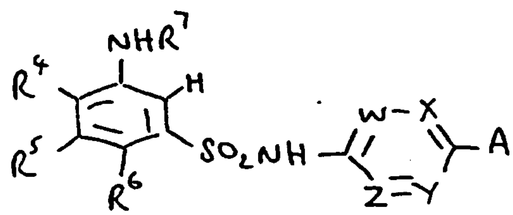
V



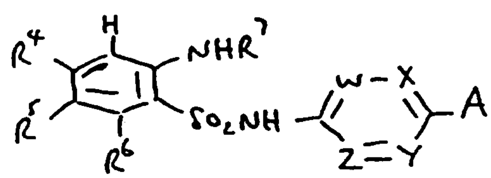
VI



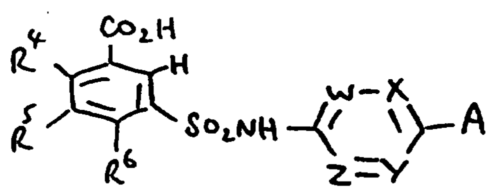
VII



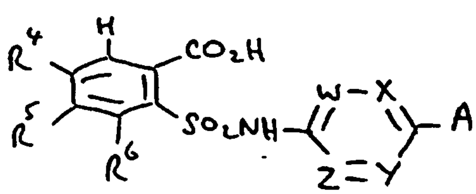
VIIIa



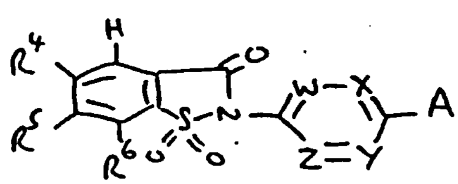
VIIIb



IXa



IXb

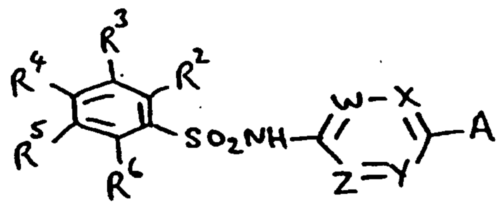


X

CLAIMS

What is claimed is:-

1. A compound of the formula I



I

wherein

one of R^2 and R^3 is a group $-Y-R^1$ and the other of R^2 and R^3 is hydrogen in which

R^1 is selected from (1-10C)alkyl, (3-8C)cycloalkyl, (3-8C)cycloalkyl(1-6C)alkyl, (2-6C)alkenyl, (2-6C)alkynyl, 9-fluorenyl, phenyl(1-6C)alkyl, naphthyl, naphthyl(1-6C)alkyl, phenyl(2-6C)alkenyl, naphthyl(2-6C)alkenyl and a group Het.$(A^1)_m$- in which m is zero or the integer one, A^1 is (1-6C)alkylene or (2-6C)alkenylene and Het is a saturated or unsaturated heterocyclic ring of 5 to 14 ring atoms, one, two or three of the ring atoms being independently selected from oxygen, nitrogen and sulphur and the remainder of the ring atoms being carbon, and in which heterocyclic ring a methylene group present is optionally replaced by a carbonyl group and/or an NH group present optionally bears an (1-4C)alkyl, phenyl or phenyl(1-4C)alkyl group; and

Y is selected from a direct bond and a group of the formula -O-, $-NR^7$.CO.O-, $-NR^7$.CO.S-, $-NR^7.CO.NR^7$-, $-NR^7.SO_2$-, -CO-, -CO.S-, $-CS.NR^7$-, -CO.O-, $-CO.NR^7$-, $-NR^7$-, $-NR^7$.CO-, $-SO_2$.O-, $-SO_2.NR^7$- and

$-S(O)_n-$ in which n is zero, 1 or 2 and R^7 is hydrogen or (1-4C)alkyl;

or R^1 is phenyl and Y is selected from a group of the formula -O-, $-NR^7.CO.O-$, $-NR^7.CO.S-$, $-NR^7.CO.NR^7-$, $-NR^7.SO_2-$, -CO-, -CO.S-, $-CS.NR^7-$, -CO.O-, $-CO.NR^7-$, $-NR^7-$, $-NR^7.CO-$, $-SO_2.O-$, $-SO_2.NR^7-$ and $-S(O)_n-$ in which n is zero, 1 or 2 and R^7 is hydrogen or (1-4C)alkyl; and wherein an alkyl, cycloalkyl, alkenyl, alkynyl, phenyl or naphthyl group of R^1, or an alkylene or alkenylene group of A^1, or a heterocyclic ring Het optionally bears one, two or three substituents independently selected from halogeno, (1-6C)alkoxy, dihalogeno(1-6C)alkoxy, trihalogeno(1-6C)alkoxy, (2-6C)alkenyloxy, phenyl(1-6C)alkoxy, hydroxy, mercapto, nitro, carboxy, (1-6C)alkoxycarbonyl, (2-6C)alkenyloxycarbonyl, phenyloxycarbonyl, phenyl(1-4C)alkoxycarbonyl, (1-6C)alkanoyl, phenyl, benzoyl, (1-6C)alkylthio, (1-6C)alkylsulphinyl, (1-6C)alkylsulphonyl, phenylthio, phenylsulphinyl, phenylsulphonyl, phenyl(1-6C)alkylthio, phenyl(1-6C)alkylsulphinyl, phenyl(1-6C)alkylsulphonyl, (1-6C)alkanoylamino, trifluoroacetyl, trifluoroacetamido, N-[(1-4C)alkyl]trifluoroacetamido, benzamido, N-[(1-4C)alkyl]benzamido, carbamoyl, (1-4C)alkylcarbamoyl, di-(1-4C)alkylcarbamoyl, phenylcarbamoyl, sulphamoyl, N-(1-4C)alkylsulphamoyl, N,N-di-(1-4C)alkylsulphamoyl, N-phenylsulphamoyl, (1-6C)alkanesulphonamido, benzenesulphonamido, ureido, 3-(1-6C)alkylureido, 3-phenylureido, thioureido, 3-(1-6C)alkylthioureido, 3-phenylthioureido and a group of the formula -NRaRb in which Ra and Rb are independently selected from hydrogen, (1-6C)alkyl, phenyl(1-4C)alkyl and (1-6C)alkyl bearing a carboxy or (1-4C)alkoxycarbonyl group, or the group -NRaRb taken together complete a 1-pyrrolidinyl, 2-oxo-1-pyrrolidinyl, 1-piperidinyl, 2-oxo-1-piperidinyl or morpholino ring;

and wherein in addition a phenyl, naphthyl or heterocyclic ring Het of R^1 may optionally bear one, two or three substituents independently selected from (1-6C)alkyl, amino(1-6C)alkyl, hydroxy(1-6C)alkyl, (1-4C)alkoxy(1-6C)alkyl, N-[(1-4C)alkyl]amino(1-6C)alkyl, N,N-[di(1-4C)alkyl]amino(1-6C)alkyl, (2-6C)alkenyl,

2-[(1-6C)alkoxycarbonyl]ethenyl, 2-phenylethenyl, (2-6C)alkynyl, (1-6C)alkoxycarbonylethynyl, phenylethynyl, halogeno(1-6C)alkyl, (1-4C)alkylthio(1-4C)alkyl, (1-4C)alkylsulphinyl(1-4C)alkyl, (1-4C)alkylsulphonyl(1-4C)alkyl, (3-6C)cycloalkyl, (3-8C)cycloalkyl(1-6C)alkyl and phenyl(1-6C)alkyl;

and wherein a phenyl ring of a substituent on R^1 may itself optionally bear one or two (1-4C)alkyl, (1-4C)alkoxy, halogeno, trifluoromethyl, nitro or cyano substituents;

R^4 is selected from hydrogen, fluoro, amino and hydroxy;

R^5 and R^6 are independently selected from hydrogen, (1-6C)alkyl, (1-6C)alkoxy, halogeno, trifluoromethyl, cyano, nitro, amino, (1-6C)alkylamino, di-(1-6C)alkylamino, (1-6C)alkanoylamino, hydroxy, mercapto, (1-6C)alkylthio, (1-6C)alkanoyl, trifluoroacetyl, trifluoroacetylamino, (1-6C)alkanesulphonamido, 1-pyrrolidinyl, 2-oxo-1-pyrrolidinyl, 1-piperidinyl, 2-oxo-1-piperidinyl or morpholino; and

the ring containing W, X, Y and Z and bearing substituent A is selected from:

(a) a ring in which W is nitrogen; X is CH; Y is nitrogen; and Z is CRy in which Ry is hydrogen, halogeno, (1-4C)alkyl or (1-4C)alkoxy; and substituent A is hydrogen, halogeno, (1-4C)alkyl, methoxy, ethoxy, methylthio, ethylthio, trifluoromethyl or ethynyl;

(b) a ring in which W is CRz in which Rz is hydrogen, halogeno, (1-4C)alkyl or (1-4C)alkoxy; X is nitrogen; Y is nitrogen; and Z is CH; and substituent A is halogeno, (1-4C)alkyl, methoxy, ethoxy, methylthio, ethylthio, trifluoromethyl or ethynyl; and

(c) a ring in which W and X are both nitrogen; Y is CH; and Z is CRx in which Rx is hydrogen, methyl, methoxy or ethoxy; and substituent A is halogeno, (1-4C)alkyl, methoxy, ethoxy, methylthio, ethylthio,

trifluoromethyl or ethynyl;

or a pharmaceutically-acceptable salt thereof; but excluding the compound N-(6-chloropyridazin-3-yl)-2-methylbenzenesulphonamide and pharmaceutically acceptable salts thereof.

2. A compound as claimed in claim 1 wherein R^1 is selected from

methyl, ethyl, propyl, isopropyl, sec-butyl, norbornyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclopropylmethyl, cyclopropylethyl, cyclobutylmethyl, cyclopentylmethyl, vinyl, allyl, 1-propenyl, 2-butenyl, ethynyl, 1-propynyl, 2-propynyl, 1-butynyl, 9-fluorenyl, benzyl, 1-phenylethyl, 2-phenylethyl, naphthyl, naphth-1-ylmethyl, naphthyl-2-ylmethyl, 1-(naphth-1-yl)ethyl, 2-(naphth-1-yl)ethyl, 2-phenylethenyl, 3-phenylpropen-1-yl, 2-(naphth-1-yl)ethenyl, 3-(naphth-1-yl)propen-1-yl and a group Het.$(A^1)_m$- in which m is zero or the integer one, A^1 is methylene, ethylene, trimethylene, propylene, vinylene or propenylene and Het is pyridyl, pyrimidinyl, pyrazinyl, pyridazinyl, triazinyl, thienyl, furyl, tetrahydrofuryl, tetrahydrothienyl, pyranyl, pyrrolyl, imidazolyl, pyrazolyl, thiazolyl, isothiazolyl, oxazolyl, isoxazolyl, indolyl, indazolyl, quinolyl, isoquinolyl, phthalazinyl, naphthyridinyl, quinoxazinyl, cinnolinyl, carbazolyl, beta-carbolinyl, phenanthridinyl, acridinyl, phenanthrolinyl, phenazinyl, phenothiazinyl, phenoxazinyl, chromanyl, isochromanyl, pyrrolidinyl, pyrrolinyl, imidazolidinyl, pyrazolidinyl, pyrazolinyl, piperidinyl, piperazinyl, indolinyl, isoindolinyl, morpholinyl, thiomorpholinyl, quinuclidinyl, 2-oxo-hexahydroazepinyl, 2-oxopyrrolidinyl, 2-oxo-tetrahydrothienyl, N-methylpiperidinyl, N-benzylpiperidinyl or N-methylmorpholinyl;

and wherein an alkyl, cycloalkyl, alkenyl, alkynyl, phenyl or naphthyl group of R^1, or an alkylene or alkenylene group of A^1, or a heterocyclic ring Het optionally bears one, two or three substituents independently selected from fluoro, chloro, bromo, iodo, methoxy, ethoxy, propoxy, difluoromethoxy, trifluoroethoxy, 2,2,2-trifluoroethoxy, 3,3,3-trifluoropropoxy, pentafluoroethoxy,

vinyloxy, allyloxy, 1-propenyloxy, 2-butenyloxy, benzyloxy, 1-phenylethoxy, 2-phenylethoxy, 2-phenylpropoxy, 3-phenylpropoxy, hydroxy, mercapto, nitro, carboxy, methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, allyloxycarbonyl, 2-methyl-2-propenyloxycarbonyl, 3-methyl-3-butenyloxycarbonyl, phenyloxycarbonyl, benzyloxycarbonyl, 1-phenylethoxycarbonyl, 2-phenylethoxycarbonyl, formyl, acetyl, propionyl, phenyl, benzoyl, methylthio, ethylthio, methylsulphinyl, ethylsulphinyl, methylsulphonyl, ethylsulphonyl, phenylthio, phenylsulphinyl, phenylsulphonyl, phenylmethylthio, 2-phenylethylthio, phenylmethylsulphinyl, 2-phenylethylsulphinyl, phenylmethylsulphonyl, 2-phenylethylsulphonyl, formamido, acetamido, propionamido, trifluoroacetyl, trifluoroacetamido, N-methyltrifluoroacetamide, N-ethyltrifluoroacetamide, benzamido, N-methylbenzamido, N-ethylbenzamido, carbamoyl, N-methylcarbamoyl, N-ethylcarbamoyl, N,N-dimethylcarbamoyl, N,N-diethylcarbamoyl, phenylcarbamoyl, sulphamoyl, N-methylsulphamoyl, N-ethylsulphamoyl, N,N-dimethylsulphamoyl, N,N-diethylsulphamoyl, N-phenylsulphamoyl, methanesulphonamido, ethanesulphonamido, benzenesulphonamido, ureido, 3-methylureido, 3-ethylureido, 3-propylureido, 3-phenylureido, thioureido, 3-methylthioureido, 3-ethylthioureido, 3-propylthioureido, 3-phenylthioureido and a group of the formula -NRaRb in which Ra and Rb are independently selected from hydrogen, methyl, ethyl, propyl, carboxymethyl, carboxyethyl, methoxycarbonylmethyl, methoxycarbonylethyl, ethoxycarbonylethyl, ethoxycarbonylethyl, methoxycarbonylpropyl, ethoxycarbonylpropyl, benzyl, 1-phenylethyl and 2-phenylethyl, or the group -NRaRb taken together complete a 1-pyrrolidinyl, 2-oxo-1-pyrrolidinyl, 1-piperidinyl, 2-oxo-1-piperidinyl or morpholino ring;

and wherein in addition a phenyl, naphthyl or heterocyclci ring Het of R^1 may optionally bear one, two or three substituents independently selected from methyl, ethyl, propyl, aminomethyl, 2-aminoethyl, hydroxymethyl, 1-hydroxyethyl, 2-hydroxyethyl, methoxymethyl, ethoxymethyl, 1-methoxyethyl, 2-methoxyethyl, 2-ethoxyethyl, 3-methoxypropyl, methylaminomethyl, methylaminoethyl, dimethylaminomethyl, 2-(dimethylamino)ethyl, vinyl, allyl,

2-methoxycarbonylethenyl, 2-ethoxycarbonylethenyl, 2-phenylethenyl, ethynyl, 2-propynyl, methoxycarbonylethynyl, ethoxycarbonylethynyl, phenylethynyl, chloromethyl, bromomethyl, fluoromethyl, dichloromethyl, difluoromethyl, trifluoromethyl, 2,2,2-trifluoroethyl, pentafluoroethyl, methylthiomethyl, 1-methylthioethyl, 2-methylthioethyl, 2-methylthioprop-2-yl, ethylthiomethyl,1-ethylthioethyl, 2-ethylthioethyl, 2-ethylthioprop-2-yl, methylsulphinylmethyl, 1-methylsulphinylethyl, 2-methylsulphinylethyl, 2-methylsulphinylprop-2-yl, ethylsulphinylmethyl, 1-ethylsulphinylethyl, 2-ethyl-sulphinylethyl, 2-ethylsulphinylprop-2-yl, methylsulphonylmethyl, 1-methylsulphonylethyl, 2-methylsulphonylethyl, 2-methylsulphonylprop-2-yl, ethylsulphonylmethyl, 1-ethylsulphonylethyl, 2-ethyl-sulphonylethyl, 2-ethylsulphonylprop-2-yl, cyclopropyl, cyclobutyl, cyclopentyl, cyclopropylmethyl, cyclopropylethyl, cyclobutylmethyl, cyclopentylmethyl, benzyl, 1-phenylethyl and 2-phenylethyl;

and wherein a phenyl ring of a substituent on R^1 may itself optionally bear one or two methyl, ethyl, methoxy, ethoxy, fluoro, chloro, bromo, iodo, trifluoromethyl, nitro or cyano substituents;

R^5 and R^6 are independently selected from hydrogen, methyl, ethyl, methoxy, ethoxy, fluoro, chloro, bromo, iodo, trifluoromethyl, cyano, nitro, amino, methylamino, ethylamino, dimethylamino, N-methyl-N-ethylamino, diethylamino, formamido, acetamido, propionamido, hydroxy, mercapto, methylthio, ethylthio, formyl, acetyl, propionyl, trifluoroacetyl, trifluoroacetylamino, methanesulphonamido, ethanesulphonamido, 1-pyrrolidinyl, 2-oxo-1-pyrrolidinyl, 1-piperidinyl, 2-oxo-1-piperidinyl and morpholino;

the ring containing W, X, Y and Z and bearing substituent A is selected from:

(a) a ring in which W is nitrogen; X is CH; Y is nitrogen; and Z is

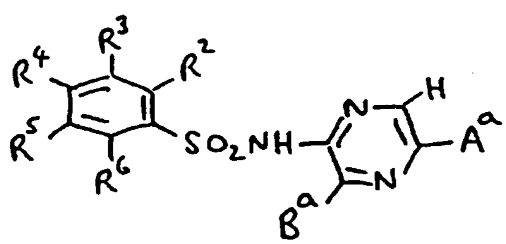
CRy in which Ry is hydrogen, hydrogen, fluoro, chloro, bromo, iodo, methyl, ethyl, propyl, methoxy, ethoxy or propoxy and

substituent A is hydrogen, chloro, bromo, iodo, methyl, ethyl, propyl, methoxy, ethoxy, methylthio, ethylthio, trifluoromethyl or ethynyl;

(b) a ring in which W is CRz in which Rz is hydrogen, hydrogen, fluoro, chloro, bromo, iodo, methyl, ethyl, propyl, methoxy, ethoxy or propoxy; X is nitrogen; Y is nitrogen; and Z is CH; and substituent A is chloro, bromo, iodo, methyl, ethyl, propyl, methoxy, ethoxy, methylthio, ethylthio, trifluoromethyl or ethynyl; and

(c) a ring in which W and X are both nitrogen; Y is CH; and Z is CRx in which Rx is hydrogen, methyl, methoxy or ethoxy; and substituent A is chloro, bromo, iodo, methyl, ethyl, propyl, methoxy, ethoxy, methylthio, ethylthio, trifluoromethyl or ethynyl.

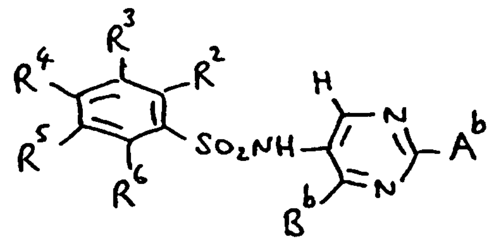
3. A compound of the formula Ia



Ia

in which A^a is hydrogen, halogeno, (1-4C)alkyl, methoxy, ethoxy, methylthio, ethylthio, trifluoromethyl or ethynyl; B^a is hydrogen, halogeno, (1-4C)alkyl or (1-4C)alkoxy; and R^2 to R^6 have any of the values defined in Claim 1 or 2; or a pharmaceutically acceptable salt thereof

4. A compound of the formula Ib



Ib

in which A^b is halogeno, (1-4C)alkyl, methoxy, ethoxy, methylthio, ethylthio, trifluoromethyl or ethynyl; B^b is hydrogen, halogeno, (1-4C)alkyl or (1-4C)alkoxy; and R^2 to R^6 have any of the values defined in Claim 1 or 2; or a pharmaceutically acceptable salt thereof.

5. A compound of the formula I as claimed in claim 1 selected from:-

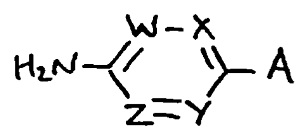
3-[N-(5-bromo-3-methoxypyrazin-2-yl)sulphamoyl]-N-tert-butylbenzamide;
3-[N-(5-bromo-3-methoxypyrazin-2-yl)sulphamoyl]-N-[2-(2-methoxyphenyl)ethyl]benzamide;
3-[N-(5-bromo-3-methoxypyrazin-2-yl)sulphamoyl-N-[2-(2-methoxyphenyl)ethyl]thiobenzamide;
3-[N-(5-bromo-3-methoxypyrazin-2-yl)sulphamoyl]-N-[3-(2-oxopyrrolidin-1-yl)propyl]benzamide;
3-[N-(2-chloro-4-methoxypyrimidin-5-yl)sulphamoyl]-N-phenethylbenzamide;
benzyl 2-[N-(5-bromo-3-methoxypyrazin-2-yl)sulphamoyl]benzoate;
4-methoxybenzyl 2-[N-(5-bromo-3-methoxypyrazin-2-yl)sulphamoyl]-benzoate;
3-chlorobenzyl 2-[N-(5-bromo-3-methoxypyrazin-2-yl)sulphamoyl]-benzoate;
2-[N-(2-chloro-4-methoxypyrimidin-5-yl)sulphamoyl]-N-(phenethyl)benzamide;
phenethyl 2-[N-(2-chloro-4-methoxypyrimidin-5-yl)sulphamoyl]benzoate;
and N-(5-bromo-3-methoxypyrazin-2-yl)-2-(phenylsulphonyl)-benzenesulphonamide; or a pharmaceutically acceptable salt thereof.

6. A salt as claimed in any one preceding claim which is selected from salts with bases forming physiologically acceptable cations and, for those compounds which are sufficiently basic, salts with acids forming physiologically acceptable anions.

7. A pharmaceutical composition which comprises a compound of the formula I, Ia or Ib, or a pharmaceutically acceptable salt thereof, as claimed in any of claims 1 to 6, together with a pharmaceutically acceptable diluent or carrier.

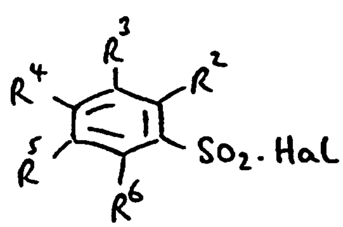
8. A process for the manufacture of a compound of formula I, or a pharmaceutically acceptable salt thereof, which is characterised in that:-

(a) an amime of formula III,



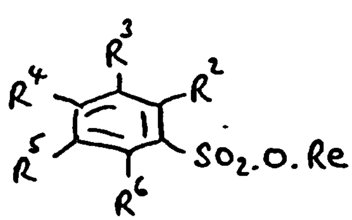
III

or an alkali metal salt thereof, is reacted with a sulphonyl halide of formula IV



IV

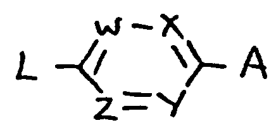
in which Hal. is a halogeno group or witha sulphonate of the formula IVa



IVa

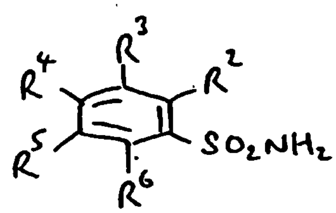
in which Re is an electron deficient phenyl group;

(b) for those compounds of formula I in which W is nitrogen, a compound of formula V



V

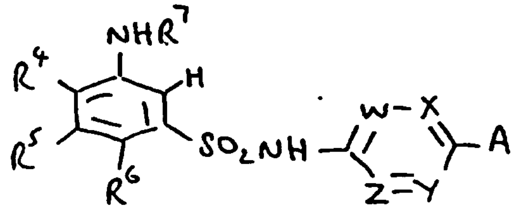
in which L is a leaving group is reacted with a sulphonamide of the formula VI



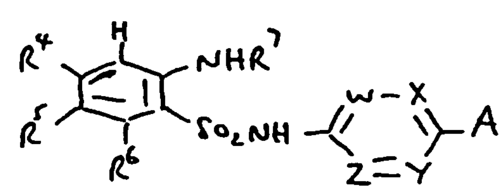
VI

or an alkali metal salt thereof; or

(c) for a compound of the formula I in which Y is a group of the formula $-NR^7.CO.O-$, $-NR^7.CO.S-$, $NR^7.CO.NH-$, $-NR^7.SO_2-$, $-NR^7-$ or $-NR^7.CO-$, a compound of formula VIIIa or VIIIb



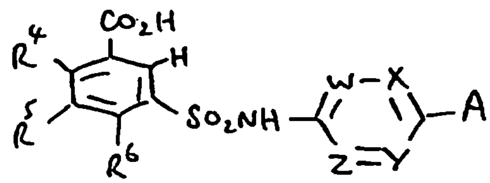
VIIIa



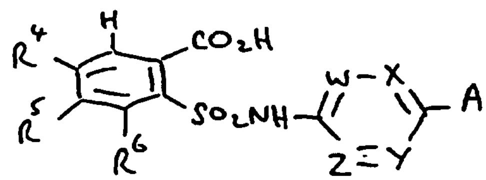
VIIIb

is alkylated or acylated with an appropriate alkylating or acylating agent;

(d) for a compound of the formula I in which Y is a group of the formula -CO.NR^7-, -CO.O- or -CO.S-, a carboxylic acid of the formula IXa or IXb



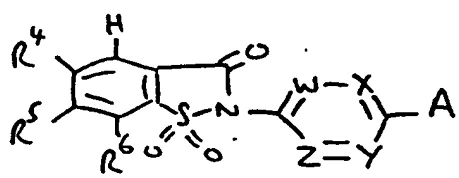
IXa



IXb

or a reactive derivative thereof, is reacted with a compound of the formula R^1.NHR^7, R^1.OH or R^1.SH;

(e) for a compound of the formula I in which R^3 is hydrogen and R^2 is a group -Y-R^1 in which Y is a group -CO.O-, -CO.S- or -CO.NR^7-, a compound of the formula X



X

is reacted with a compound of the formula R^1.OH, R^1.SH or R^1.NHR^7;

whereafter a compound of the formula I may be converted into another compound of formula I by conventional functional group interconversion;

whereafter a protecting group, if present, may be removed;

whereafter when a pharmaceutically acceptable salt of a compound of formula I is required, it is obtained by reaction with the appropriate

acid or base affording a pysiologically-acceptable ion, or by any other conventional salt formation procedure;

whereafter when an optically active form of a compound of formula I is required, one of the aforesaid processes (a)-(e) may be carried out using an optically active starting material, or the racemic form of a compound of formula I is resolved;

and wherein the radicals have any of the meanings defined in any of claims 1-4 unless otherwise stated.

HC70020
JJH 26OCT95

The Patent Office

63

Application No: GB 9524401.8
Claims searched: 1-8

Examiner: Stephen Quick
Date of search: 13 February 1996

Patents Act 1977
Search Report under Section 17

Databases searched:

UK Patent Office collections, including GB, EP, WO & US patent specifications, in:

UK Cl (Ed.O): (not searched)

Int Cl (Ed.6): (not searched)

Other: Online: CAS ONLINE

Documents considered to be relevant:

Category	Identity of document and relevant passage		Relevant to claims
X	EP0514133 A1	(MERCK SHARP & DOHME), see especially page 12 (line 21ff), example 22 (page 26) and page 11 (line 39)	1-8

X	Document indicating lack of novelty or inventive step	A	Document indicating technological background and/or state of the art.
Y	Document indicating lack of inventive step if combined with one or more other documents of same category.	P	Document published on or after the declared priority date but before the filing date of this invention.
		E	Patent document published on or after, but with priority date earlier than, the filing date of this application.
&	Member of the same patent family		